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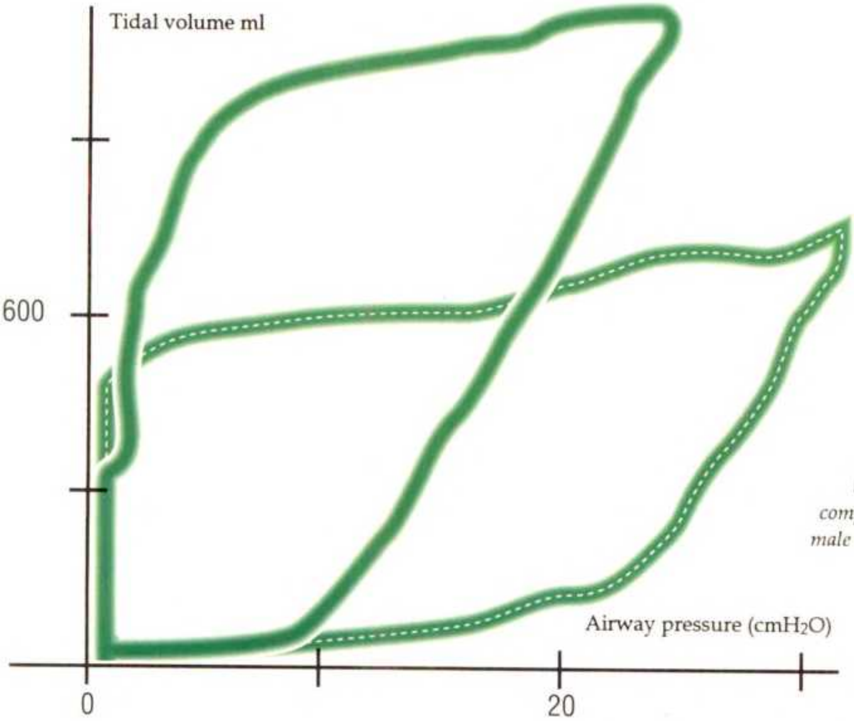

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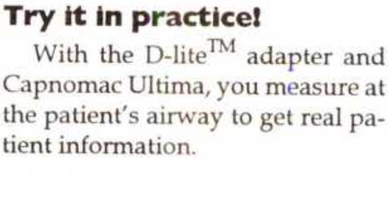

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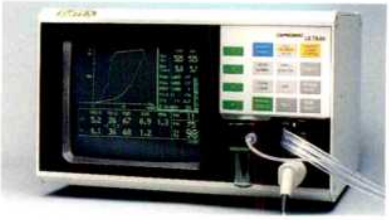

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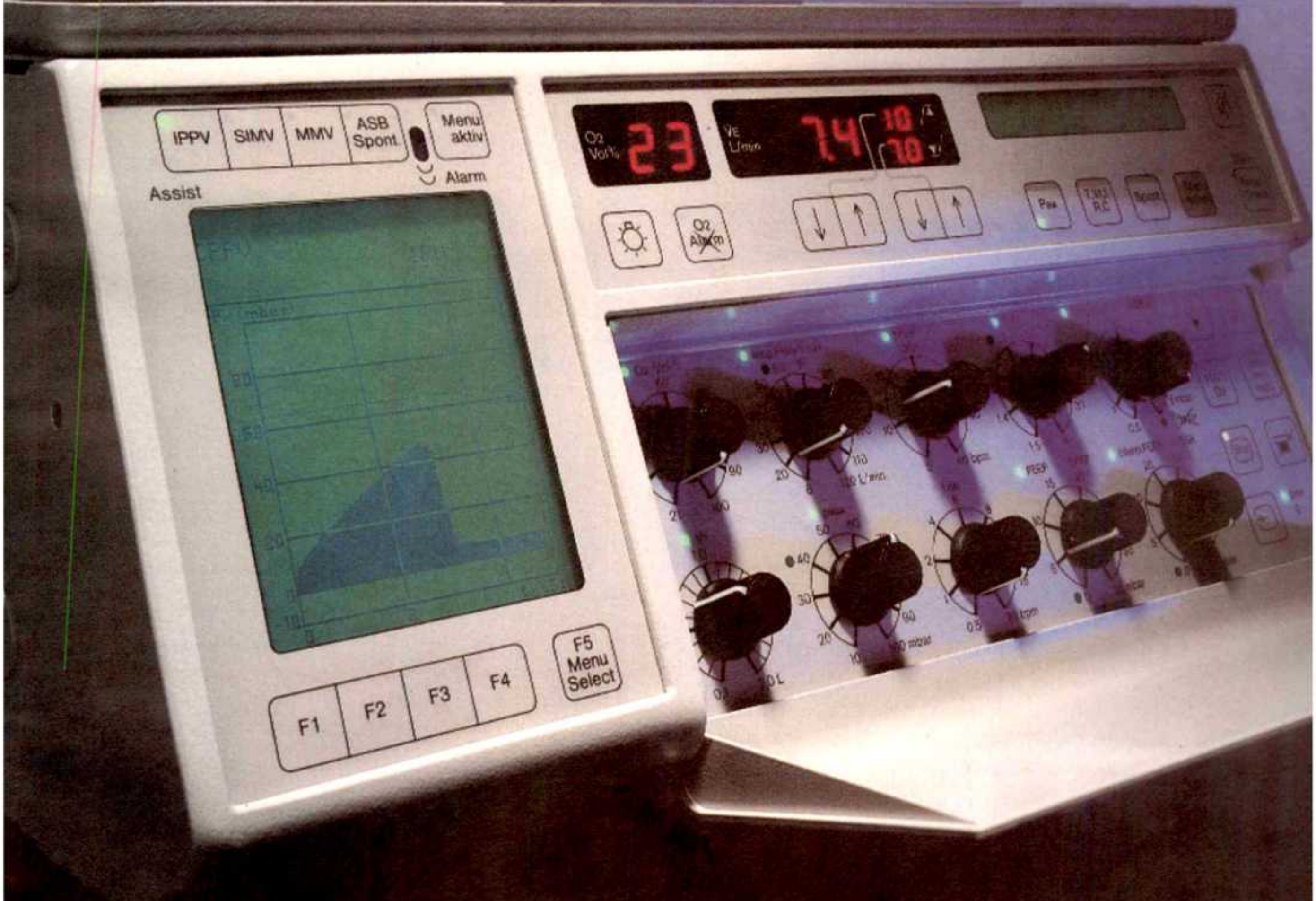

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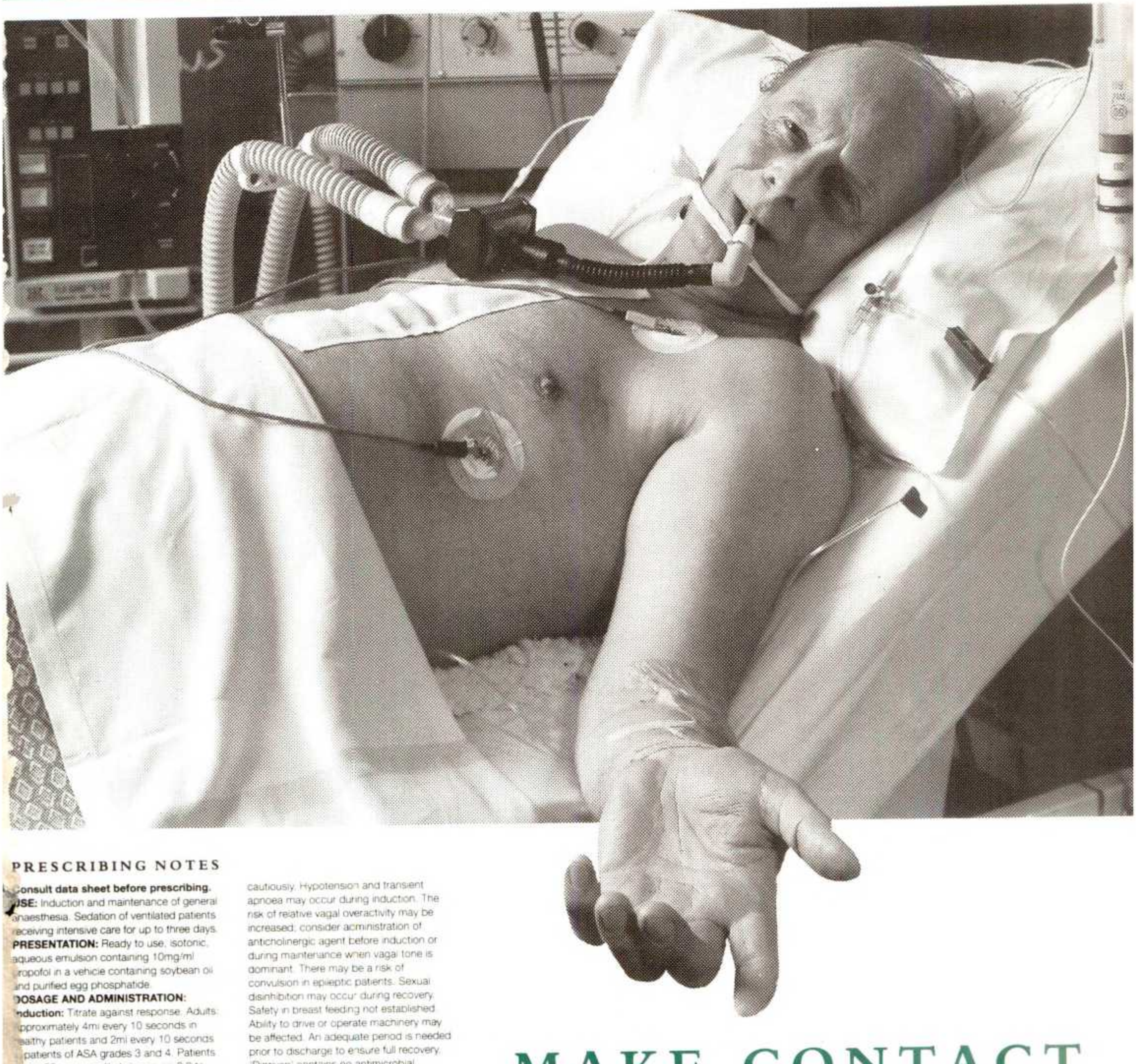

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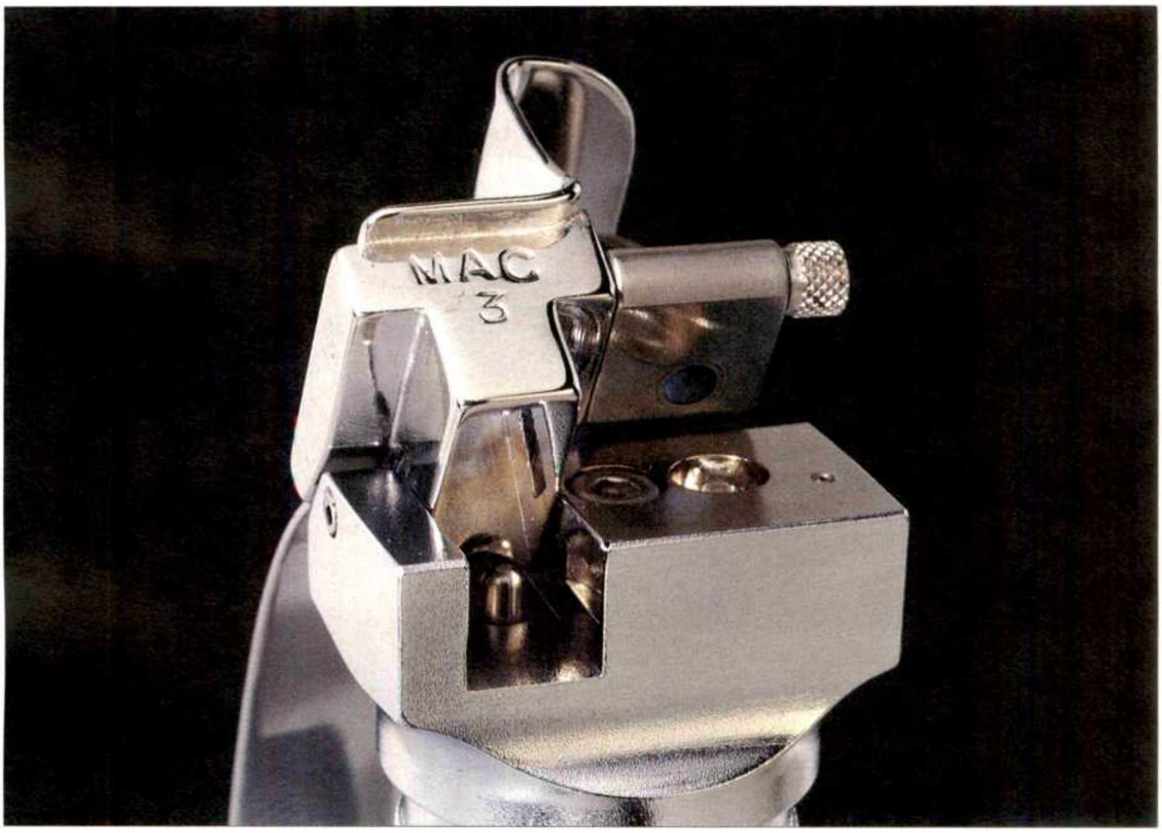

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THE EPIC STUDY

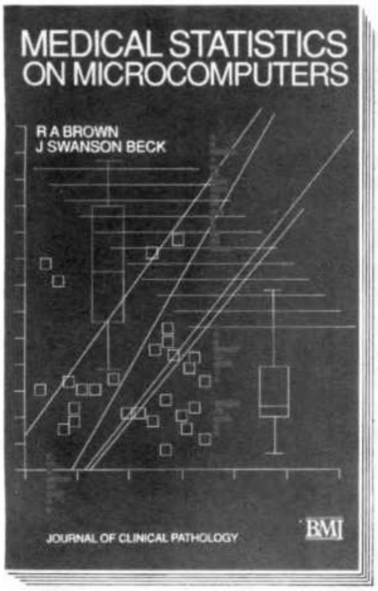
April 29, 1992

The European Prevalence of Infection in Intensive Care (EPIC) Study Advisory Committee, with representatives in 17 countries, is calling on all intensive care units in the U.K. and Western Europe to participate in the EPIC Study, the first pan-European point prevalence study of nosocomial infection in intensive care units. On April 29, 1992, ICUs in 17 countries will be involved in the collection of data which will provide a "snapshot" of ICU infection and associated risk factors.

At the recent launch of the EPIC Study, Professor Peter Suter, president of the World Federation of Societies of Intensive Care, stressed the importance of participating in the study. "Not every-one is aware of how important nosocomial infections are in terms of costs of increased mortality and morbidity associated with them and financial implications," he said.

The EPIC Study has been planned in response to the need for collaborative efforts towards improved surveillance, working towards identifying appropriate directions for infection control procedures which will effectively address the growing issue of nosocomial infection in ICUs. The EPIC Study is open to all units in western Europe.

Further details on participation are available from: The EPIC Study Co-ordinator, Medical Action Communications Ltd, Action International House, Crabtree Office Village, Eversley Way, Thorpe, Egham, Surrey TW20 8RY, U.K.



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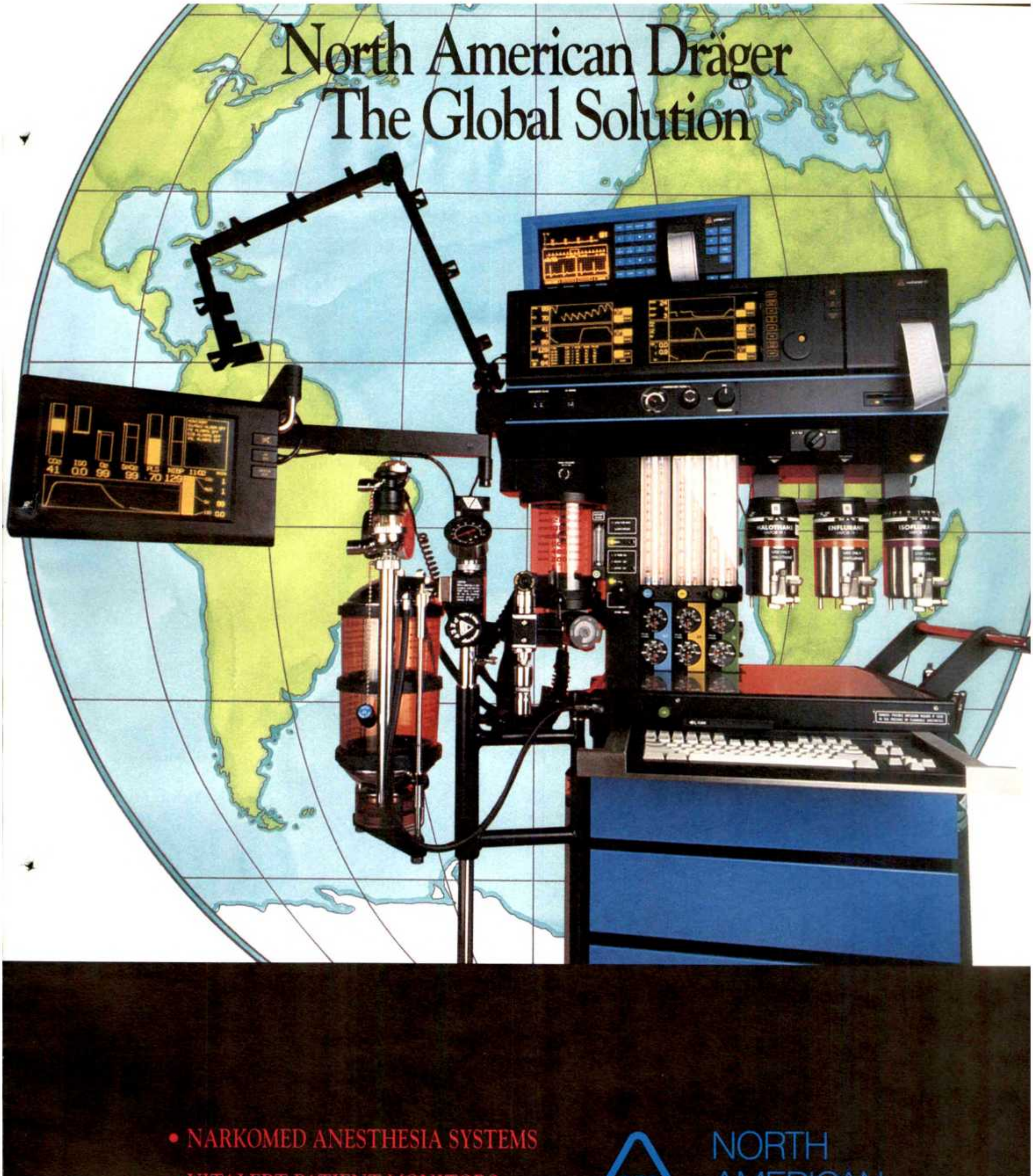

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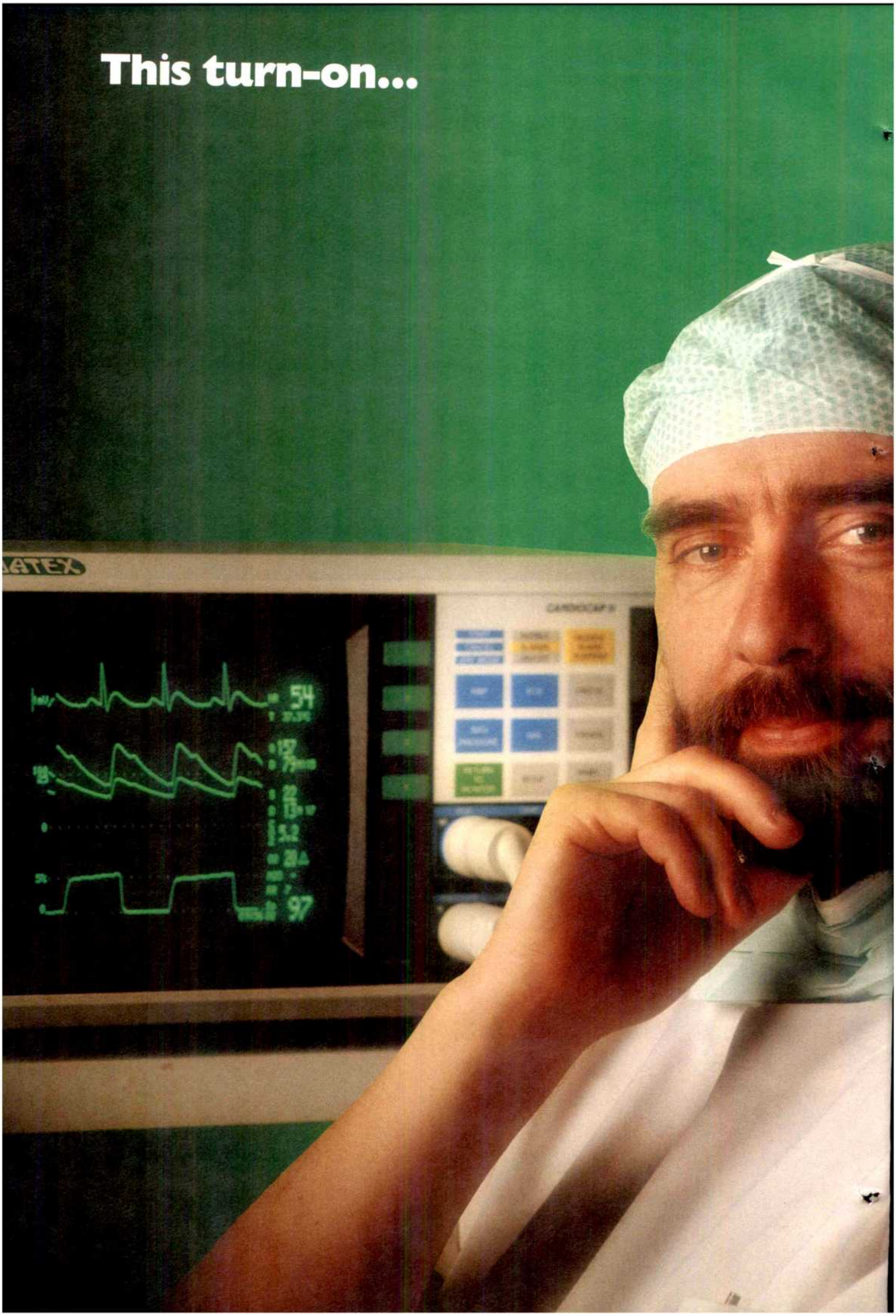
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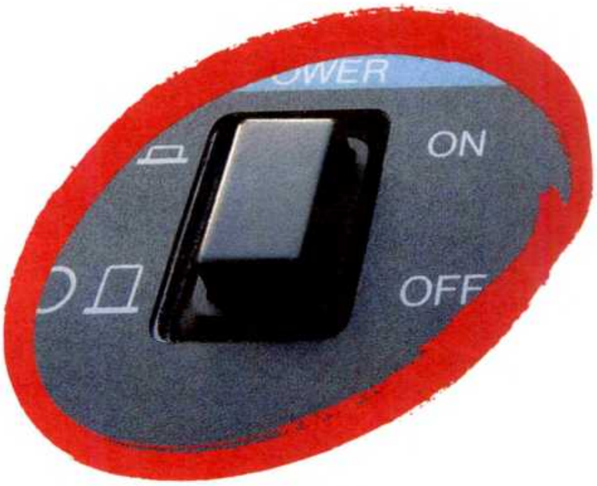

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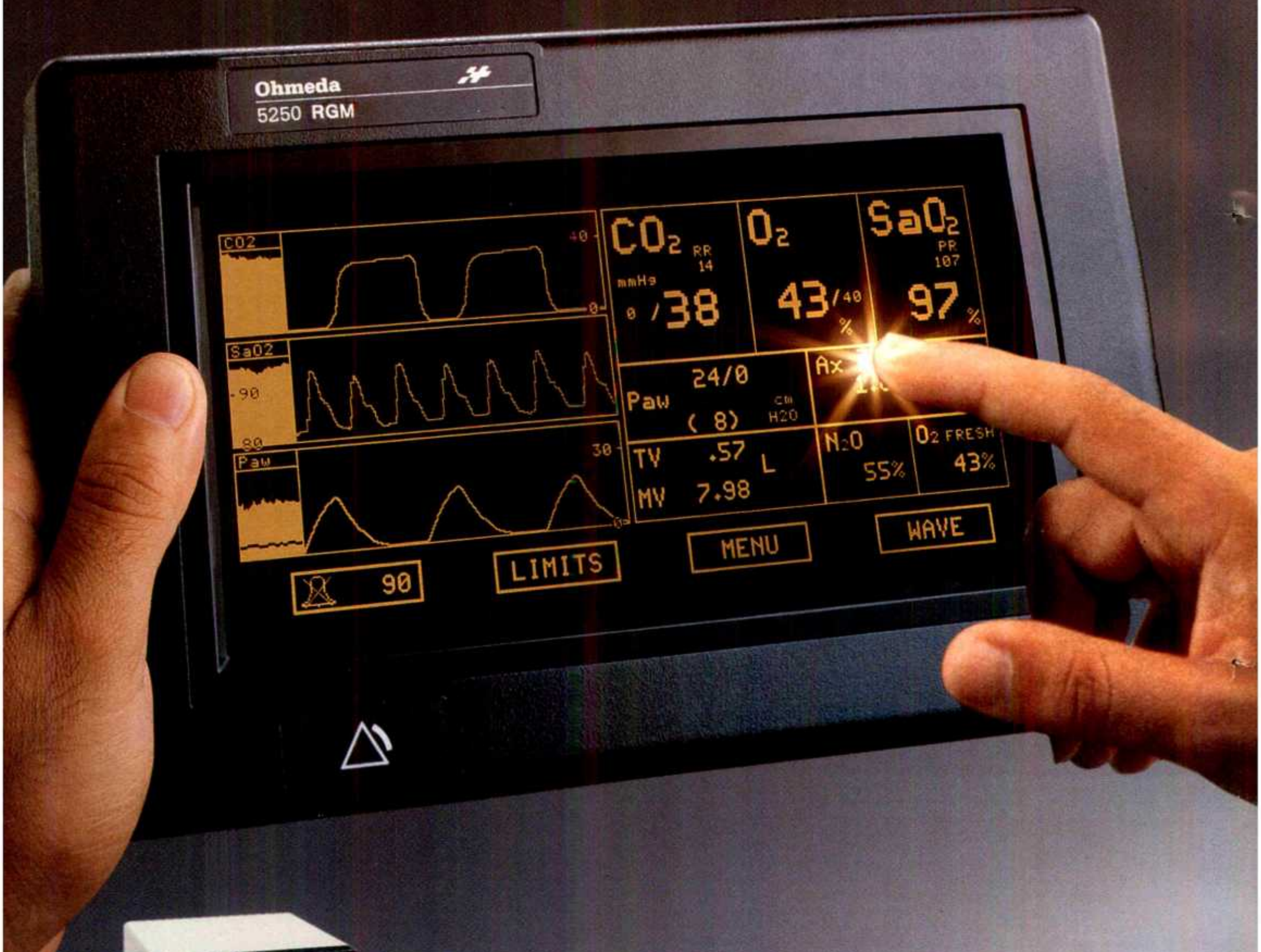

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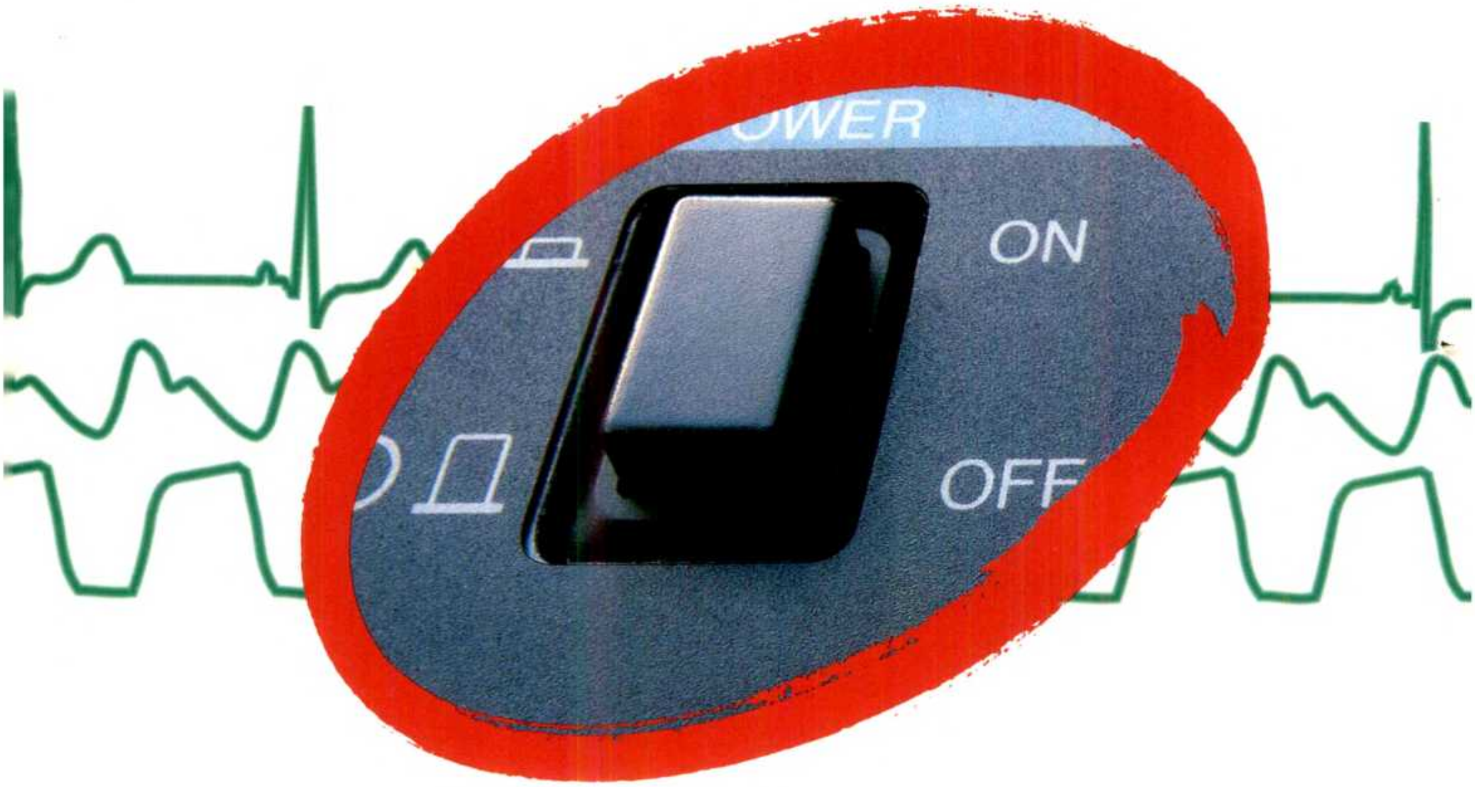

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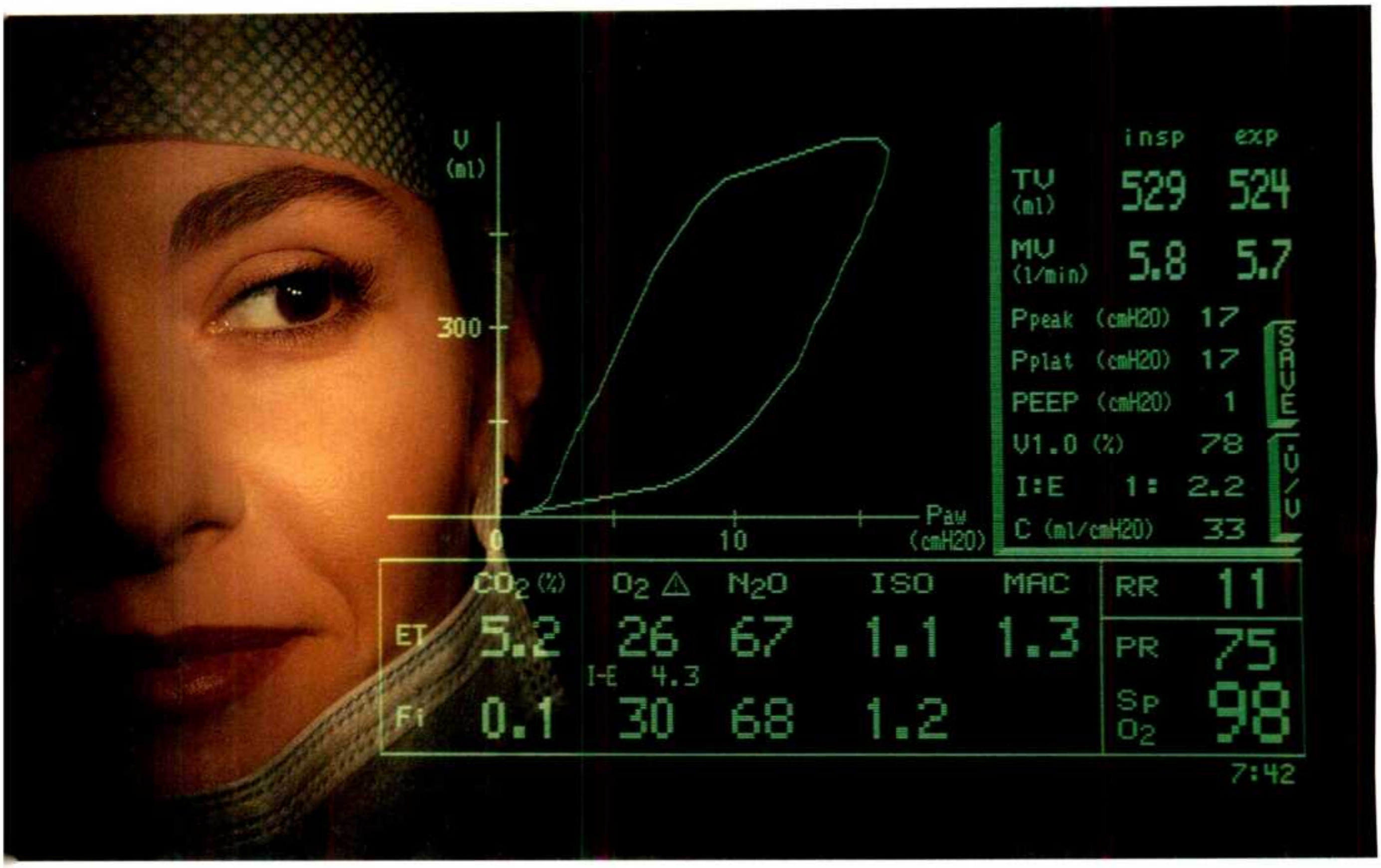

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BRITISH JOURNAL OF ANAESTHESIA

VOLUME 68, No. 4 APRIL 1992

EDITORIAL

THE DEVELOPMENT AND SAFE USE OF PATIENT-CONTROLLED ANALGESIA

The concept of patient-controlled analgesia (PCA) was developed simultaneously and independently in the late 1960s by workers in the U.S.A. and U.K. In 1968, Philip Sechzer published a technique for the "objective measurement of pain" [1]. Patients recovering from surgery were instructed to press a button when they felt pain. When the button was pressed, a nurse observer administered 1 ml of a pethidine- or morphine-containing solution and recorded its effect on the patient. This technique enabled him to conclude that pain after surgery varied considerably between subjects and differed with the site of operation. Although this paper was concerned primarily with the measurement of pain, it was concluded also that the "analgesic demand system is excellent for treatment of postoperative pain". Sechzer recalled later that the idea occurred to him whilst attending a conference in 1965 [2] and that "the behaviour of patients controlling their own analgesia could be structured in a fashion analogous to that of an animal terminating a painful stimulus by pressing a bar".

Pioneering work was being performed at the same time by James Scott in the U.K. [3]. In 1969, he delivered to the American Association of Obstetricians and Gynaecologists a lecture in which he described a hand-held, spring-loaded clamp which controlled the rate of infusion of a 500-ml bottle of 5% glucose to which was added pethidine 300 mg. The patient was instructed to press the clamp until pain relief was obtained. He commented that if the patient "should fall asleep under the influence of meperidine (pethidine), the clamp closes automatically". He described this system as "patient controlled meperidine administration".

More sophisticated devices were described shortly after these reports. They controlled the rate of administration of i.v. analgesia by solenoid valves [4], roller pumps [5] and syringe drivers [6]. The first devices available commercially were developed in the U.K. The "Cardiff palliator" [7] was a syringe-driven device used originally on patients in labour, and the "On Demand Analgesia Computer", developed by Hull and his colleagues and later marketed by Janssen, was a microprocessor-operated system incorporating several fail-safe mechanisms [8].

Despite these developments, PCA continued to be used principally as a research tool. It was used clinically by a handful of enthusiasts only and its use on the labour ward was superseded by the advent of effective and reliable extradural services.

However, with the popularity of acute pain services in the U.S.A. and advances in microchip technology, PCA underwent a renaissance in the 1980s [9]. Two types of electronic PCA machine were developed: complicated electronic bedside machines with facilities for detailed printouts, and small "walkman-like" portable systems. In this issue of *British Journal of Anaesthesia*, workers at the Royal Hospital for Sick Children, Glasgow have evaluated the use of the Baxter disposable PCA device in children [10]. The cycle of development of PCA machines has therefore turned full circle, as this device relies on a spring-loaded clamping mechanism similar to that described by Scott in 1970 [3], albeit in a miniature and disposable form. The Baxter and Graseby electronic devices were compared in 20 children after major surgery. Pain and sedation scores, morphine consumption and oxyhaemoglobin saturations were very similar in both groups. These findings concur with those reported recently in women after gynaecological surgery [11]. It is likely that this disposable device will be extremely useful in the management of postoperative pain.

The clinical use of PCA in the U.K. has become popular and widespread only in the past 2 years. The report of the working party of the College of Anaesthetists and Royal College of Surgeons on Pain after Surgery, published in September 1990, highlighted the need for improved postoperative pain management [12]. This report has been received well and most hospitals in the U.K. are implementing its recommendations. Consequently, there has been an enormous growth in the use of PCA and it is becoming established as an accepted and desirable method of pain relief.

However, as the technique is used more frequently, problems associated with its use become evident. These complications should not limit the use of PCA, provided that those involved in the care of postoperative patients are aware of them and are prepared to follow the recommendations of the joint College working party.

Hypoxaemia is likely to occur when opioids are administered for postoperative analgesia; PCA is no exception. Hypoxaemia associated with PCA has been documented, but it is likely to be less severe when compared with extradural opioids [13]. However, hypoxaemia is associated with i.m. administration also [13, 14] and provisional data suggest that it may even be more likely compared with PCA after upper abdominal surgery. Data presented at a recent meeting of the Anaesthetic Research Society demonstrated hypoxaemia ($Sa_{O_2} < 94\%$ for more

(925781

than 12 min h^{-1}) in 12 of 20 patients receiving i.m. analgesia compared with 8 of 19 patients receiving PCA [15].

Unfortunately, the design of many electronic PCA devices is such that errors in programming are relatively easy to make. This can lead to inappropriate bolus doses and lockout times which may result in severe respiratory depression [16]. Larger doses can be administered accidentally when empty syringes or cartridges are being replaced [16]. The use of a one-way valve at the junction of the infusion and PCA tubing is obviously essential, and it is important also that this valve is inserted correctly. The importance of using antisyphon valves was demonstrated when a crack in a syringe of morphine used in a PCA machine was responsible for the rapid syphoning of the syringe contents directly into the patient [17].

The relative safety of PCA relies on the fact that the patient, and only the patient, presses the button. Severe respiratory depression is more likely if well meaning observers such as nurses or relatives take an active part in opioid administration.

Malfunctions of electronic PCA devices have occurred and in some cases resulted in delivery of large unwanted doses of opioids. Manufacturers now claim that their pumps are fail-safe, but many more hours of patient use are required before these claims can be substantiated. Indeed, in this issue of *British Journal of Anaesthesia*, a letter appears describing serious malfunctions of a PCA pump [18].

Hypovolaemia is relatively common after surgery and respiratory depression may occur in this situation if the size of the bolus dose is not reduced [19].

PCA is a major advance in the treatment of pain after surgery but, in common with all opioid techniques, may be associated with life-threatening complications. However, it should be possible to use PCA safely and effectively on the wards of most hospitals if the recommendations of the working party of the College of Anaesthetists and Royal College of Surgeons are observed. These include continuous in-service training programmes for medical and nursing staff, systematic recording of pain, sedation and ventilatory frequency, clear identification of the personnel responsible for pain relief, establishment of some form of acute pain team and continuous availability of suitably trained staff to deal with emergencies. Finally, mistakes in programming complicated PCA devices are still likely to occur occasionally and many anaesthetists would appeal to the manufacturers of PCA devices to develop machines of simple design that would minimize the possibility of programming error.

D. J. Rowbotham
Associate Editor

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ORIGINAL ARTICLES

FRESH GAS REQUIREMENTS OF AN ENCLOSED AFFERENT RESERVOIR BREATHING SYSTEM IN ANAESTHETIZED, SPONTANEOUSLY VENTILATING CHILDREN

G. MEAKIN, A. D. JENNINGS, P. C. W. BEATTY AND T. E. J. HEALY

SUMMARY

We have determined the minimum fresh gas flow rate ($\dot{V}_F$) for use with the Ohmeda enclosed afferent reservoir breathing system (EAR) in 10 anaesthetized children breathing spontaneously. First, we determined the $\dot{V}_F$ required to prevent rebreathing as detected by increased total ventilation ($\dot{V}_E$) and end-tidal carbon dioxide partial pressure. Second, we used a mathematical model to calculate the degree of rebreathing occurring at each $\dot{V}_F$. A $\dot{V}_F$ equal to the predicted alveolar ventilation was sufficient to prevent clinically detectable rebreathing in all pateints. From the model, no rebreathing occurred when $\dot{V}_F/\dot{V}_E$ was 0.78 or more. We have shown previously that the EAR functions efficiently during controlled ventilation with a $\dot{V}_F = 0.6 \times \text{weight}^{0.5}$. As this $\dot{V}_F$ is slightly greater than the predicted alveolar ventilation, we suggest that the EAR may be used with a $\dot{V}_F = 0.6 \times \text{weight}^{0.5}$ regardless of the mode of ventilation.

KEY WORDS

Anaesthesia: paediatric. Equipment: breathing systems, EAR system.

In an earlier study we assessed the efficiency of the Ohmeda enclosed afferent reservoir breathing system (EAR) during controlled ventilation in children [1]. The system was found to be highly efficient, and required a fresh gas flow ($\dot{V}_F$) close to normal alveolar ventilation to maintain normocapnia. However, to qualify as a universal breathing system, the EAR should be equally efficient during spontaneous ventilation. Therefore, we were interested to determine the minimum $\dot{V}_F$ required to prevent rebreathing when the EAR was used in anaesthetized children breathing spontaneously.

APPARATUS

As the Ohmeda EAR has been described in detail previously [1, 2], only a brief description is given here.

Fresh gas enters a rising bellows enclosed in a transparent plastic container on the inspiratory limb of the system (fig. 1). The expiratory limb passes back to a one-way valve situated at the base of the container. During inspiration, the patient breathes from the bellows and the inspiratory limb, but is prevented from breathing gas in the expiratory limb by closure of the one-way valve. On expiration, gas passes back into the inspiratory limb until the bellows is full, whereupon the one-way valve opens allowing gas to be vented. Thus the EAR functions as a Mapleson A system with a distal expiratory valve [3].

Two sizes of bellows were used in this study. The smaller (capacity 350 ml) was used for children younger than 9 yr, whilst the standard adult bellows (capacity 1500 ml) was used for older children. In all subjects, 15-mm diameter inspiratory and expiratory tubing was used in place of the standard 22-mm diameter tubing of the adult system.

SUBJECTS AND METHODS

After obtaining Ethics Committee approval we studied 10 children aged 3–13 yr and ASA class I. The age, weight and height of each child was used to calculate normal total ventilation ($\dot{V}_{tot}$) from a nomogram [4] (table I). Premedication for younger inpatients consisted of oral trimeprazine 3 mg kg^{-1} (maximum 90 mg) 2 h before operation, while patients of weight greater than 30 kg received diazepam 10 mg and droperidol 5 mg orally, 1 h before operation. Day-case patients did not receive premedication. In all patients, anaesthesia was induced with thiopentone 6–8 mg kg^{-1} followed by suxamethonium 2 mg kg^{-1}. The trachea was intubated with an uncuffed tracheal tube of appropriate size and sealed with a throat pack. Anaesthesia was maintained with approximately 66% nitrous oxide and 1.5–2% halothane in oxygen. The inspired halothane concentration was adjusted to obtain adequate anaesthesia at the initial $\dot{V}_F$ and was kept constant thereafter. Heart rate, arterial pressure and tissue oxygen saturation were monitored throughout, and a heated water mattress and warm air blower

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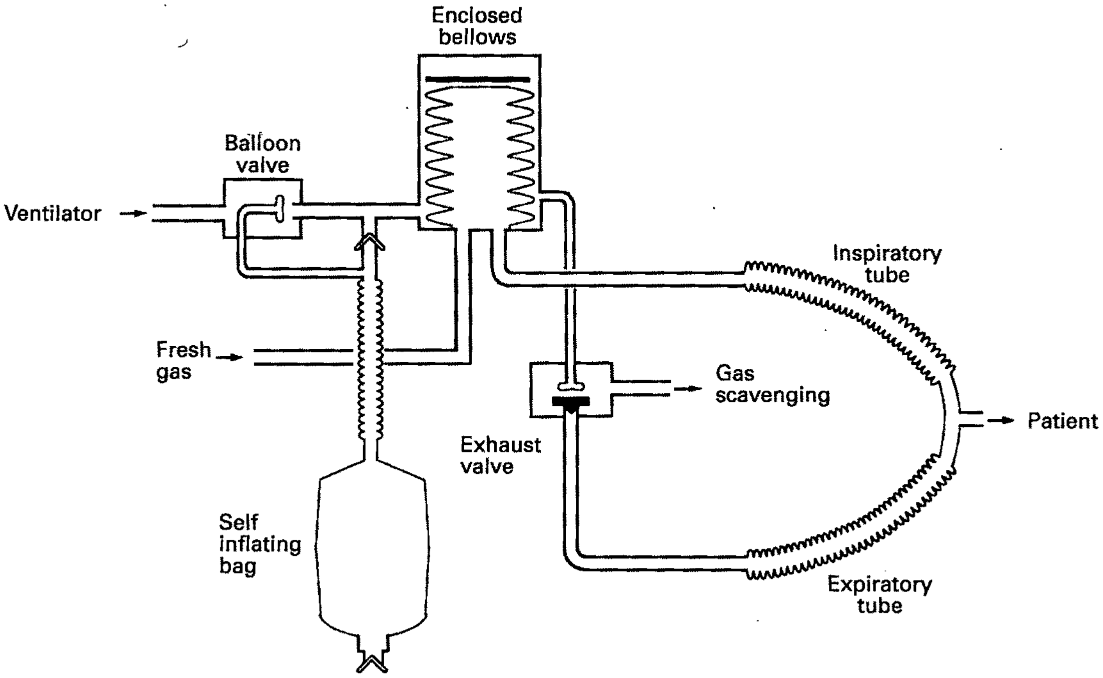

FIG. 1. Enclosed afferent reservoir breathing system.

TABLE I. *Patient characteristics*

Patient No.	Age (yr)	Weight (kg)	Height (m)	$\dot{V}$tot (litre min^{-1})	Operation
1	5	19.5	1.13	3.6	Hypospadias repair
2	6	23.0	1.20	3.9	Exploration of hand
3	13	42.3	1.43	5.1	Change of hip spica
4	4	20.7	1.17	3.9	Removal of wires R elbow
5	5	15.0	0.98	2.7	Wound redressing, change of plaster
6	5	22.0	1.20	4.0	Circumcision
7	11	36.0	1.42	4.7	Bone marrow biopsy, long line
8	4	14.3	0.98	2.9	Correction of squint
9	3	15.6	0.97	2.9	Excision of lesion L finger
10	13	55.0	1.70	6.6	Removal of wires, change of plaster

were used to maintain rectal temperature greater than 36.5 °C.

Ventilatory flow was measured using a heated pneumotachograph (Fleish No. 1) situated between the patient and the breathing system. The flow signal was integrated electronically to obtain tidal volume (VT) and expired volume ($\dot{V}$E). Respiratory gases were sampled continuously at the connector end of the tracheal tube and carbon dioxide concentration was measured using an infra-red carbon dioxide analyser (Datex Cardiocap II). Sampling by the capnograph resulted in the loss of 150 ml min^{-1} from the system, which was compensated by increasing $\dot{V}$F. All data were recorded on a three-channel pen recorder (Gould 8188).

The onset of clinical rebreathing was determined from measurements of $\dot{V}$E and end-tidal carbon dioxide tension ($P\mathrm{E}'_{\mathrm{CO_2}}$). $\dot{V}$F was set initially at a value sufficiently high for small changes to have no effect on $\dot{V}$E or $P\mathrm{E}'_{\mathrm{CO_2}}$. Thirty minutes after the start of anaesthesia and at least 15 min after the initial surgical stimulus, baseline values of $\dot{V}$E and $P\mathrm{E}'_{\mathrm{CO_2}}$ were recorded. Fresh gas flow was then reduced stepwise until one or more of the following criteria of rebreathing were satisfied [5]:

(a) an increase in $\dot{V}$E of 10% or more, not accompanied by a corresponding decrease in $P\mathrm{E}'_{\mathrm{CO_2}}$, or
(b) an increase in $P\mathrm{E}'_{\mathrm{CO_2}}$ of 0.7 kPa (5.25 mm Hg) or more, which could not be accounted for by a decrease in ventilation, or
(c) an increase in ventilation of 5% or more, accompanied by an increase in $P\mathrm{E}'_{\mathrm{CO_2}}$ of 0.3 kPa (2.25 mm Hg) or more.

Each new $\dot{V}$F was maintained for at least 5 min, allowing sufficient time to detect changes in $\dot{V}$E or $P\mathrm{E}'_{\mathrm{CO_2}}$. When such changes occurred, $\dot{V}$F was maintained until the patient's recordings were stable for a period of 60 s. In order to facilitate comparison of data from patients of different sizes, $\dot{V}$F and $\dot{V}$E were normalized by dividing by $\dot{V}$tot.

In order to calculate the volume of alveolar gas which was rebreathed at each $\dot{V}$F, a mathematical model was constructed using patient data. Assuming that the system functions as a modified Mapleson A

TABLE II. *Measured and derived respiratory data. R = values of $\dot{V}\mathrm{F}$ at which one or more clinical criteria of rebreathing were satisfied*

Patient No.	$\dot{V}\mathrm{F}:\dot{V}\mathrm{tot}$	$\dot{V}\mathrm{E}:\dot{V}\mathrm{tot}$	$P\mathrm{E}'_{\mathrm{CO_2}}$ (kPa)	$\dot{V}\mathrm{F}:\dot{V}\mathrm{E}$	$V\mathrm{R}\,\%\,V\mathrm{T}$
1	0.97	0.72	8.0	1.35	0
	0.69	0.75	7.8	0.92	0
	0.61	0.81	8.0	0.75	6
	0.50	0.78	8.0	0.64	13
	0.44R	0.92	8.1	0.48	27
	0.42R	1.07	8.1	0.39	41
	0.39R	1.03	8.4	0.38	43
2	1.00	1.24	6.9	0.81	0
	0.71	1.24	7.1	0.57	5
	0.61	1.33	6.9	0.46	16
	0.53R	1.43	7.2	0.37	34
	0.49R	1.49	7.4	0.33	34
	0.45R	1.48	7.7	0.30	46
3	1.00	0.63	7.3	1.59	0
	0.71	0.73	6.6	0.97	0
	0.59	0.60	7.0	0.98	0
	0.50	0.60	7.2	0.83	0
	0.44	0.58	7.5	0.76	0
	0.38	0.67	7.5	0.57	22
	0.33	0.64	7.8	0.52	22
	0.30R	0.68	8.0	0.44	33
4	1.13	0.87	7.1	1.30	0
	0.71	0.83	7.3	0.86	0
	0.61	0.90	7.5	0.68	0
	0.53R	0.96	7.8	0.55	8
5	1.13	0.93	8.7	1.22	0
	0.70	1.11	8.4	0.63	0
	0.59R	1.11	8.9	0.53	0
	0.48R	1.19	9.1	0.40	23
	0.43R	1.25	9.4	0.34	24
	0.37R	1.24	9.6	0.30	41
6	0.76	0.93	6.7	0.82	0
	0.59	0.98	6.7	0.60	0
	0.49	0.95	6.9	0.52	18
	0.44R	1.00	7.0	0.44	28
	0.34R	0.97	7.5	0.35	31
7	0.71	0.92	6.6	0.77	0
	0.61	0.93	6.8	0.66	0
	0.50	0.95	6.6	0.53	13
	0.44R	1.02	6.9	0.43	29
	0.40R	1.15	7.0	0.35	46
8	1.00	1.20	7.2	0.83	0
	0.82	1.13	7.3	0.73	0
	0.72	1.15	7.5	0.63	0
	0.61	1.19	7.7	0.51	0
	0.51	1.14	7.8	0.45	30
	0.40R	1.20	8.1	0.33	35
9	1.00	1.17	6.7	0.85	0
	0.61	1.15	7.0	0.53	20
	0.58	1.21	7.1	0.48	16
	0.47	1.20	7.1	0.39	23
	0.42R	1.41	7.4	0.30	43
10	0.89	0.75	6.9	1.19	0
	0.70	0.76	6.9	0.92	0
	0.60	0.78	7.1	0.77	0
	0.51	0.78	7.2	0.65	0
	0.40	0.78	7.5	0.51	9
	0.34R	0.85	7.6	0.40	17
	0.31R	0.95	7.6	0.33	35

and there is no longitudinal mixing of expired gas fractions, rebreathing of alveolar gas should occur only when $\dot{V}\mathrm{F}$ is less than the alveolar ventilation [3]. Thus for one ventilatory cycle:

$$V\mathrm{R} = V\mathrm{A} - V\mathrm{F} \qquad (1)$$

where $V\mathrm{R}$ = volume of rebreathed alveolar gas; $V\mathrm{A}$ = volume of expired alveolar gas; $V\mathrm{F}$ = volume of fresh gas entering the system; but

$$V\mathrm{A} = V\mathrm{T} - V\mathrm{D} \qquad (2)$$

where $V\mathrm{T}$ = tidal volume; $V\mathrm{D}$ = anatomical plus apparatus deadspace.

Substituting for $V\mathrm{A}$ in equation (1) and rearranging:

$$V\mathrm{R} = V\mathrm{T} - (V\mathrm{D} + V\mathrm{F}) \qquad (3)$$

Anatomical and apparatus deadspace was determined by Fowler's method [6] as follows. The flow and capnograph signals were aligned by identifying the point of end-expiration. Expired carbon dioxide concentration was plotted against volume expired, and deadspace was determined by moving a vertical line along the x-axis (volume expired) until the areas between the line and the sigmoid portion of the curve were equal. The rebreathed volume, expressed as a percentage of the tidal volume ($V\mathrm{R}\,\%\,V\mathrm{T}$), was plotted against the $\dot{V}\mathrm{F}:\dot{V}\mathrm{E}$ ratio, and a curve fitted by the method of least squares using the Technicurve statistical package (Ashton Scientific) on an Compaq 286 computer.

RESULTS

Data are expressed as mean (SEM).

The values of $\dot{V}\mathrm{E}$, $P\mathrm{E}'_{\mathrm{CO_2}}$ and the calculated degree of rebreathing for each tested $\dot{V}\mathrm{F}$ are shown in table II. Rebreathing was not detected clinically until $\dot{V}\mathrm{F}$ was reduced to less than 0.7 $\dot{V}\mathrm{tot}$, which corresponded to a $\dot{V}\mathrm{F}:\dot{V}\mathrm{E}$ ratio of 0.63 (patient 5, table II). At lesser flow rates, rebreathing was detected by an increase in $\dot{V}\mathrm{E}$ alone or in combination with an increase in $P\mathrm{E}'_{\mathrm{CO_2}}$ in nine patients, and by an increase in $P\mathrm{E}'_{\mathrm{CO_2}}$ alone in one patient.

The mean respiratory variables immediately before and after the clinical criteria of rebreathing were satisfied are shown in table III. Rebreathing was detected when mean $\dot{V}\mathrm{F}:\dot{V}\mathrm{E}$ was reduced to 0.43 (0.03), and the mean $V\mathrm{R}\,\%\,V\mathrm{T}$ was 25 %.

The calculated degree of rebreathing ($V\mathrm{R}\,\%\,V\mathrm{T}$) was related inversely to $\dot{V}\mathrm{F}:\dot{V}\mathrm{E}$ and, in the model, a value of at least 0.78 was required to eliminate rebreathing completely (fig. 2).

DISCUSSION

Our finding that rebreathing was detected by clinical criteria when mean $\dot{V}\mathrm{F}:\dot{V}\mathrm{E}$ was reduced to 0.43 (0.03) agrees with the results obtained by Kain and Nunn using a standard Mapleson A system (0.43 (0.03)) [5]. However, mean $\dot{V}\mathrm{F}:\dot{V}\mathrm{E}$ immediately before the onset of clinical rebreathing was somewhat less than that obtained by these authors (0.51 (0.03) *vs* 0.71 (0.04)). The greater specificity of our study for the rebreathing point is probably explained by the

TABLE III. *Respiratory data immediately before and after clinical criteria of rebreathing were satisfied*

	$\dot{V}_F:\dot{V}_{tot}$	$\dot{V}_E:\dot{V}_{tot}$	$P_{E'_{CO_2}}$ (kPa)	$\dot{V}_F:\dot{V}_E$	$V_R\,\%\,V_T$
Before ($n = 10$)					
Mean	0.51	0.98	7.5	0.53	14
SEM	0.03	0.07	0.2	0.03	3
Min.	0.33	0.64	6.6	0.39	0
Max.	0.70	1.33	8.4	0.68	30
After ($n = 10$)					
Mean	0.44	1.06	7.7	0.43	25
SEM	0.03	0.07	0.2	0.03	4
Min.	0.30	0.68	6.9	0.30	0
Max.	0.59	1.43	8.9	0.55	43

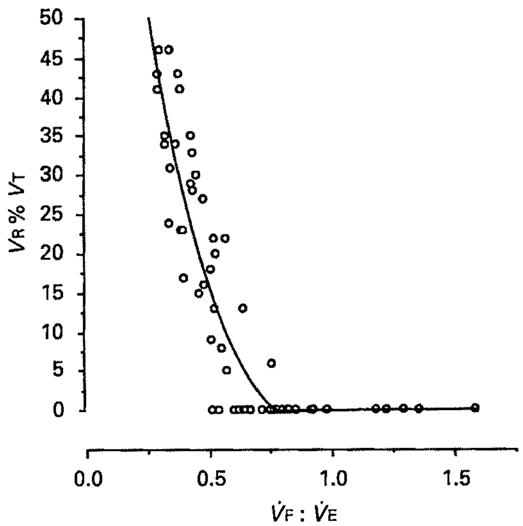

FIG. 2. Relationship between the degree of rebreathing ($V_R\,\%\,V_T$) and the fresh gas flow rate to total ventilation ratio ($\dot{V}_F:\dot{V}_E$).

larger average number of test flows per patient (six *vs* four), which resulted in smaller incremental changes in $\dot{V}_F$.

Our results are also consistent with those of Norman, Adams and Sykes [7], Conway and colleagues [8] and Alexander [9], who showed that the standard A system can function without evidence of rebreathing with fresh gas flows close to the patient's alveolar ventilation (60–70 % $\dot{V}_E$). This degree of efficiency is possible because afferent reservoir systems allow selective venting of alveolar gas, while conserving deadspace gas to take part in subsequent gas exchange [3].

It has been claimed by Humphrey [10] that resiting the expiratory valve of the standard A system on the anaesthetic machine, as in the Lack and EAR systems, improves efficiency by reducing the amount of mixing of gas in the inspiratory tube. This suggestion is not supported by our results with the EAR, nor by those of Chan, Bruce and Soni who found little difference in the $\dot{V}_F:\dot{V}_E$ ratio at the onset of rebreathing with the Mapleson A, Lack and EAR systems when compared using a lung model [11]. Moreover, these authors showed that the use of the minimum inspired concentration of carbon dioxide to detect rebreathing—the method used by Humphrey—resulted in much smaller values of $\dot{V}_F:\dot{V}_E$ at the point of rebreathing than those obtained using end-tidal carbon dioxide concentrations, and that the results were more variable. This method has been criticized by Sykes, who noted that a minimum carbon dioxide concentration of zero at some point in the ventilatory cycle does not indicate the absence of rebreathing [12]. This is true particularly of the afferent reservoir systems, in which the presence of only a small amount of deadspace gas in the inspiratory tube may give a minimum inspired carbon dioxide concentration of zero, despite considerable alveolar gas rebreathing.

We determined also the onset of rebreathing from a mathematical model (fig. 2). This method is not dependent on observing physiological changes, so rebreathing can be demonstrated at an early stage. However, it is necessary to assume that there is negligible longitudinal mixing of gas in the delivery tube. As separation of gas fractions is a prerequisite for efficiency with the EAR, and we have shown recently that fractional utilization of fresh gas may reach 92 % under optimal conditions of controlled ventilation, this assumption would appear to be reasonable [1]. The $\dot{V}_F:\dot{V}_E$ ratio of 0.78 at the onset of rebreathing in figure 2 is comparable to the results obtained by Miller in three studies of afferent reservoir systems using a mechanical lung model (0.85, 0.68 and 0.76) [13, 14].

In our earlier study, we developed a simple formula for use with the EAR during controlled ventilation of children [1]. When $\dot{V}_E:\dot{V}_F$ was maintained greater than 1.5, $\dot{V}_F = 0.6 \times \text{weight}^{0.5}$ was shown to produce normocapnia or mild hypocapnia in children aged 1–16 yr. We showed also that the formula gave values of $\dot{V}_F$ which were slightly greater than the normal alveolar ventilation (0.7 $\dot{V}_{tot}$). Our data demonstrate that $\dot{V}_F = 0.7\ \dot{V}_{tot}$ was sufficient to prevent the appearance of clinical changes associated with rebreathing in all of our spontaneously ventilating patients. These results suggest that the EAR may be used safely and efficiently in anaesthetized children with a $\dot{V}_F = 0.6 \times \text{weight}^{0.5}$, regardless of the mode of ventilation. It may be described, therefore, as a universal anaesthetic breathing system.

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EXTRADURAL CLONIDINE INFUSIONS FOR ANALGESIA AFTER TOTAL HIP REPLACEMENT

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SUMMARY

We have examined the effectiveness of extradural clonidine infusions for postoperative analgesia and the effect of clonidine on extradural morphine. In a double-blind, controlled study, patients, undergoing total hip replacement were allocated randomly to receive one of two doses of extradural clonidine (25 µg h⁻¹ or 50 µg h⁻¹), low dose extradural morphine or a combination of morphine and clonidine. Pain scores in the morphine group were significantly greater than in the clonidine groups ($P < 0.01$) and the combination group ($P < 0.05$) during the first 1 h after surgery. The requirements for systemic analgesia were least in the combination and larger dose clonidine group, and the duration of effect of the initial bolus dose was significantly longer compared with the morphine and low dose clonidine groups ($P < 0.05$). Arterial pressure was reduced in the clonidine groups, although the incidence of clinical hypotension was low. There were no significant differences between the groups in emetic symptoms or urinary retention.

KEY WORDS

Anaesthetic techniques: extradural. Analgesia: postoperative. Analgesics: morphine. Sympathetic nervous system: α adrenergic agonists, clonidine.

As a result of the discovery of an adrenergic pain modulating system in the spinal cord [1], alpha$_2$ adrenergic agonists have been used in the management of postoperative pain. Although the analgesic properties of the alpha$_2$ adrenergic agonists have been well documented in both animal studies and clinical trials [2, 3], duration and efficacy are variable [4, 5].

Castro and co-workers assessed the physical properties, pharmacokinetics and dynamics of clonidine after i.v., extradural and intrathecal administration in sheep [6]. They concluded that extradural administration was the most appropriate route, and infusions were superior to bolus injections.

The main side effects associated with the extradural use of clonidine are sedation, hypotension and a marked reduction in salivary flow. These properties are dose related [7–9], within therapeutic limits.

Clonidine is a complex drug [10]. Alpha$_2$ receptors at spinal cord level are thought to be responsible for the analgesic properties [11], and for the depressant effects on the cardiovascular system [12]. Although clonidine produces hypotension by a central effect, peripheral alpha$_1$ and alpha$_2$ receptors are thought to be responsible for some of the cardiovascular changes after extradural administration. Alpha$_2$ depressant effects predominate at smaller plasma concentrations, whereas alpha$_1$ pressor effects are found with greater doses. Previous studies on oral clonidine have demonstrated that anxiolysis could be achieved with minimal effects on the cardiovascular system [13]. Therefore, it may be possible to produce satisfactory analgesia without significant hypotension. In addition, synergism between alpha adrenergic and opioid systems has been suggested [14], although the precise mechanism is unclear. The benefit of such an interaction may lie in the potential to treat pain by precise manipulation of different receptors to achieve analgesia with a minimum of side effects.

The aim of this study was to examine the analgesic efficacy of clonidine administered by extradural infusion. As synergism between opioids and alpha$_2$ adrenergic agonists has been suggested, clonidine was combined with a low dose of extradural morphine; a group which received extradural morphine only was included for comparison.

PATIENTS AND METHODS

After obtaining local Ethics Committee approval and informed patient consent, we studied patients (ASA grade I or II, aged 30–75 yr, weights 50–100 kg) undergoing total hip replacement under general anaesthesia. Patients were excluded if they were receiving any medication other than mild oral analgesics, or if there was any contraindication to extradural block.

Patients were premedicated with oral temazepam 20 mg 60–90 min before operation. On arrival of the patient in the anaesthetic room, an i.v. cannula was inserted and non-invasive arterial pressure, heart rate and tissue oxygen saturation monitoring

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commenced using the Hewlett–Packard 78554A monitor, with a continuous printout. Before induction of anaesthesia, an extradural catheter was sited at L1–2 or L2–3, using a standard 16-gauge Portex minipack. To test for accidental intrathecal insertion of the catheter, 1.5% plain lignocaine 3 ml was administered and sensation tested with ice to exclude subarachnoid block. A standardized general anaesthetic was administered, using thiopentone 4 mg kg^{-1} and fentanyl 1.5 μg kg^{-1} for induction; neuromuscular block was provided by vecuronium 0.1 mg kg^{-1}, and anaesthesia was maintained with 1–1.5% isoflurane, with 65% nitrous oxide in oxygen, with intermittent positive pressure ventilation to normocapnia.

During insertion of the femoral component of the hip prosthesis (approximately 30 min before the end of surgery), patients were allocated randomly to receive one of four treatments via the extradural catheter:

(1) clonidine 150 μg (1 ml) diluted to 10 ml in 0.9% saline, followed by an extradural infusion of clonidine 25 μg ml^{-1};

(2) clonidine 150 μg (1 ml) diluted to 10 ml in 0.9% saline, followed by an extradural infusion of clonidine 50 μg ml^{-1};

(3) morphine 1 mg diluted to 10 ml in 0.9% saline, followed by an infusion of extradural morphine 0.1 mg ml^{-1};

(4) clonidine 150 μg (1 ml) plus morphine 1 mg diluted to 10 ml with 0.9% saline followed by an extradural infusion of morphine 0.1 mg ml^{-1}.

In all groups, the rate of infusion was set at 1 ml h^{-1}, and was commenced immediately after the bolus injection and continued for 24 h after surgery. The injections and infusions were prepared and administered by an operator who had no further part in the study.

At the end of the procedure, residual neuromuscular block was antagonized and the patient allowed to wake up quietly. During the initial 1 h after operation, patients recovered in a theatre recovery ward and for the remainder of the 24-h study period, they were nursed in a high dependency unit.

Arterial pressure and heart rate were recorded at 10-min intervals for the first 1 h, and thereafter at 1-h intervals for 12 h. Systolic pressure less than 85 mm Hg was treated initially with ephedrine 5 mg i.v., repeated if required. Mean arterial pressure was calculated from the formula: diastolic pressure plus one-third (systolic − diastolic pressure). A heart rate of < 45 beat min^{-1} was treated with atropine 0.3 mg i.v.

All assessments of sedation and pain were made by the first author, who was unaware of the nature of the extradural injection or infusion. In the recovery ward, patients were assessed on a three-point scale (awake, drowsy or asleep) at 30 and 60 min.

Pain was assessed at 30 and 60 min after surgery by the observer, on a four-point scale (no pain, mild, moderate or severe pain). After objective assessment at 30 and 60 min, patients completed a 100-mm VAS for pain (no pain at one extreme and worst possible pain at the other).

In all patients, a separate i.v. cannula was inserted in the non-infused arm for use with a patient controlled analgesia system (PCAS), set to provide boluses of morphine 1 mg with an initial lockout time of 20 min and no fixed dose limit. The lockout time was adjusted as required to ensure that analgesia was adequate. Effectiveness of analgesia was assessed by the total requirements from the PCAS during the first 24 h after surgery. In addition, the time from extradural administration of the test drug during operation until the time of the first use of PCAS after operation was recorded.

Postoperative blood loss was measured by weighing swabs and recording suction loss and replaced promptly with colloid and packed cells.

Haemoglobin oxygen saturation was monitored continuously and ventilatory frequency was noted at 15-min intervals during the 24-h study.

The incidence of nausea or vomiting, urinary retention requiring catheterization and any spontaneously volunteered side effects were recorded.

Results are presented as mean (SD) for parametric data, and median and range for non-parametric data. Statistical analysis was by repeated measures analysis of variance (ANOVA), Mann–Whitney *U* test and chi square. Statistical significance was assumed at $P < 0.05$.

RESULTS

The four groups were comparable in age, weight and height (table I). The male to female ratio was not distributed evenly among the groups, with the clonidine 25 μg ($P < 0.05$) and combination ($P < 0.05$) groups having a larger number of female patients compared with the two other groups.

There were no significant differences between the groups with respect to the MAP values immediately before extradural injection (fig. 1).

With between-group analysis, MAP was significantly less in the combination group compared with the other groups from 5 min after extradural injection until 20 min after injection ($P < 0.05$). During the period from 30 min to 2 h after operation, arterial pressure was significantly greater in the morphine group compared with the three other groups ($P < 0.01$). At 18 and 24 h after surgery, arterial pressure was significantly less in both the clonidine groups than in the morphine and combination groups ($P < 0.05$).

On within-group analysis, MAP was significantly less in both the clonidine groups compared with preinduction values from 15 min after extradural injection to the end of the study ($P < 0.05$). In the morphine group, the values for MAP were significantly smaller than baseline from 10 to 30 min after injection ($P < 0.05$). The MAP values in the combination group were significantly smaller than the preinduction value for the period from 5 to 30 min after injection ($P < 0.05$).

During the first 90–120 min after extradural injection, three, one and two patients in the clonidine 25 μg, morphine and combination groups, respectively, required vasoconstrictor therapy to correct systolic pressure less than 85 mm Hg. In all cases,

TABLE I. *Patient characteristics (mean* (SD *or range)).* *P < 0.05 *compared with clonidine 50 μg and morphine groups*

	Clonidine 25 mg	Clonidine 50 μg	Morphine	Clonidine +morphine
n	25	25	25	25
Age (yr)	61 (43–75)	64 (45–75)	67 (38–75)	63 (41–75)
Weight (kg)	67 (10)	72 (12)	70 (14)	68 (11)
Height (cm)	158 (5)	160 (6)	162 (4)	159 (7)
Sex (M:F)	5:15*	9:11	10:10	2:18*

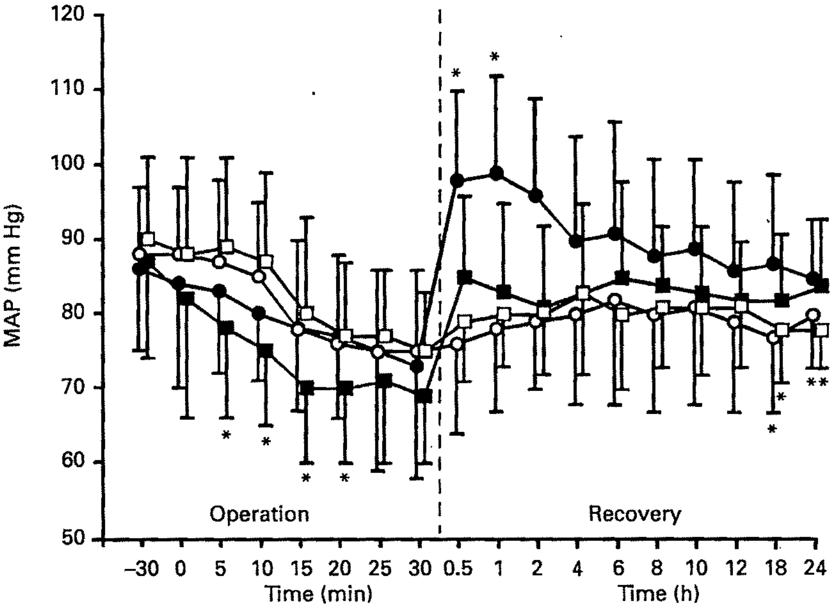

FIG. 1. Changes in mean arterial pressure (MAP) during the study period (mean, SD). −30 = Pre-induction value; 0 = administration of extradural test drug. *$P < 0.05$ compared with other groups. ○ = clonidine 25 μg; □ = clonidine 50 μg; ● = morphine; ■ = combination.

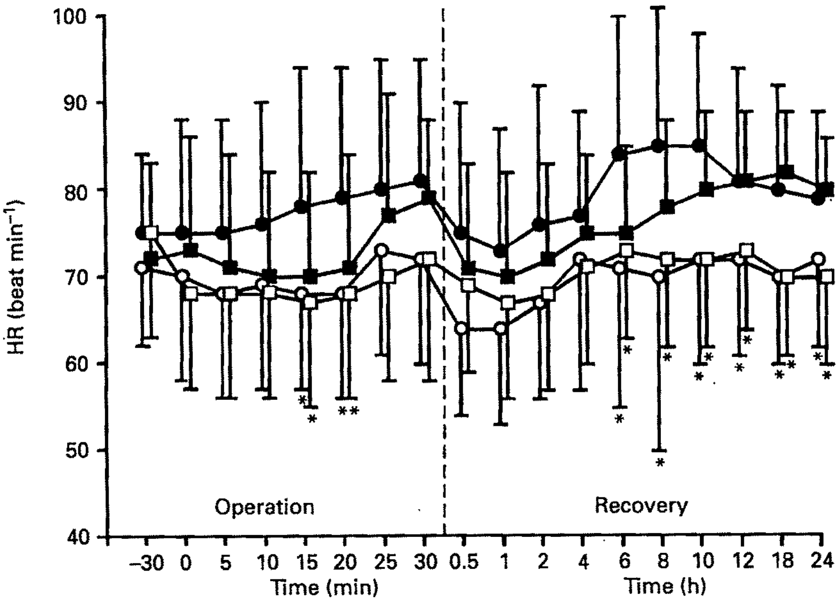

FIG. 2. Changes in heart rate (HR) during the study period (mean, SD). −30 = Pre-induction value; 0 = administration of the extradural test drug. *$P < 0.05$ compared with morphine group. ○ = clonidine 25 μg; □ = clonidine 50 μg; ● = morphine; ■ = combination.

one dose of ephedrine 5 mg was sufficient to correct the hypotension and no further treatment was required.

There were no significant differences in heart rate between the groups in the period immediately before injection. The values for heart rate were significantly smaller in both the clonidine groups compared with the morphine group at 15 and 20 min after injection, and from 6 to 24 h after operation ($P < 0.05$) (fig. 2).

On within-group analysis, the heart rate values during the first 1 h after surgery in the clonidine 25 μg group were significantly smaller than baseline

TABLE II. *Sedation scores.* *$P < 0.05$ *compared with morphine group*

	Clonidine 25 μg		Clonidine 50 μg		Morphine		Clonidine +morphine	
	30 min	60 min	30 min	60 min	30 min	60 min	30 min	60 min
Awake (No.)	10*	10	6	6	1	6	8*	12
Drowsy (No.)	8*	7	9	12	15	11	12	8
Asleep (No.)	2	3	5	2	4	3	0	0

TABLE III. *Analgesia (mean (SD or range)).* $P < 0.05$: * *compared with morphine group*; † *compared with clonidine 25 μg and morphine groups*

	Clonidine 25 μg	Clonidine 50 μg	Morphine	Clonidine +morphine
PCAS morphine (mg)	14.5 (7)	10.5 (6)*	15.9 (11)	9.3 (6)†
Time to first use PCAS (min)	144 (99)	286 (112)†	109 (99)	283 (120)†
No PCAS needed (No. patients)	0	2	1	3
VAS at 30 min	23 (0–75)*	8 (0–40)*	49 (0–90)	24 (0–80)*
VAS at 60 min	24 (0–65)*	18 (0–65)*	45 (0–89)	25 (0–65)*

TABLE IV. *Side effects*

	Clonidine 25 μg	Clonidine 50 μg	Morphine	Clonidine +morphine
Nausea/vomiting (No.)	7/1	1/0	5/2	6/0
Urinary retention (No.)	2	1	4	5

($P < 0.05$). There were no significant differences from baseline in the other groups. No patients required treatment for bradycardia.

At 30 min, but not 60 min, after surgery, significantly more patients in the morphine group were either drowsy or asleep, compared with the clonidine 25 μg and combination groups ($P < 0.05$) (table II).

At 30 min, significantly more patients in the morphine group (seven) had moderate pain compared with the clonidine 25 μg (three) and clonidine 50 μg (zero) groups. Four patients in the combination group had moderate pain, but this was not significant compared with the other three groups. By 60 min, the morphine group had a significantly greater number of patients with moderate pain (10) compared with the other three groups (one, two and one patients in the clonidine 25 μg, clonidine 50 μg and combination groups, respectively).

Subjective assessment of pain was similar. At both 30 and 60 min after operation, all three groups had significantly smaller values for pain compared with the morphine group (table III). No patient was unable to co-operate with the VAS scoring system.

The time from administration of the bolus extradural dose to the first self administration of analgesia via the PCAS was taken as an indication of the duration of action of the bolus dose. This period in the clonidine 50 μg and combination groups was significantly longer than in both the clonidine 25 μg and the morphine groups (table III).

Total morphine administered via the PCAS was recorded for the first 24 h after surgery. Morphine requirements in the combination group were significantly less than the morphine and clonidine 25 μg group. PCAS requirements in the clonidine 50 μg group were significantly less than in the extradural morphine group. There were no other significant differences between the groups (table III).

There were no significant differences between the groups in the incidence of emetic symptoms or urinary retention requiring catheterization (table IV).

One patient in each of the morphine and combination groups had a ventilatory frequency of less than 10 b.p.m. during the study period. In the patient in the morphine group, this was associated with a decrease in haemoglobin oxygen saturation to 88%, and occurred 5 min after use of the PCAS.

Five patients in the clonidine 25 μg and seven patients in the clonidine 50 μg groups experienced dryness of the mouth. No patient in either the morphine or combination group reported a dry mouth.

DISCUSSION

In the combination and clonidine 50 μg groups, PCAS requirements were least and the duration of analgesic effect of the bolus doses was greatest. Postoperative pain scores and PCAS requirements were greatest in the extradural morphine group.

The dose of extradural morphine used here was small ($0.1\ \mathrm{mg\ h^{-1}}$) and the PCAS was provided to ensure adequate analgesia after operation. By choosing such a small dose of morphine, the demonstration of increased analgesia by the addition of clonidine was possible. Potentiation of both local anaesthetic agents and opioids by clonidine has been suggested by other workers [15, 16] and, although the evidence is often conflicting [17], the clinical implications are demonstrated in this study. The effect of an inadequate bolus dose and subsequent infusion of extradural morphine was improved significantly by the addition of clonidine to the bolus dose. Although the work of Reddy, Maderdrut and Yaksh has presented a clearer picture of the interactions at a spinal cord level [18], the exact mechanism of the interaction between the $alpha_2$ adrenergic agonists and other drug groups is still unclear. Other agents such as serotonin may also be important [19], although it is possible that they act by sharing common final pathways with the $alpha_2$ adrenergic agonists [20].

It has been suggested that analgesia attributable to the $alpha_2$ adrenergic agonists alone is insufficient, and that their role lies in reducing the dose requirements of other agents [21]. Analgesia associated with bolus extradural doses has been shown to be dose related, although the cardiovascular effects are less predictable at the extremes of the dosing range [22]. In addition, the variability in duration of analgesic effect has led to the suggestion that extradural clonidine may be more effectively administered by infusion rather than bolus doses. It would appear from our study that clonidine infusions used alone can provide satisfactory postoperative analgesia and with the greater dose infusion the systemic analgesic requirements were less than in the low-dose group.

One of the commonest side effects associated with clonidine is sedation, but this was not apparent in our study, even with the greater infusion rate. However, the dry mouth often associated with oral clonidine used for hypertension [23] was noted in both the clonidine groups.

The smaller arterial pressure in both clonidine groups compared with baseline readings are probably attributable to the reduction in central sympathetic outflow [24]. Heart rate changes with clonidine are less predictable and there was no apparent dose-related reduction in heart rate noted here. Blood loss was monitored in the perioperative period and replaced promptly, so the cardiovascular changes that occurred after the extradural bolus dose were caused probably by the drug administered rather than inadequate fluid balance. The cardiovascular changes associated with the combination group were less marked than in the clonidine groups, which reflects the smaller plasma concentration of clonidine in this group.

One of the disadvantages associated with the use of spinal and extradural opioids is the relatively high incidence of urinary retention leading to catheterization [25]. As the urinary tract has been implicated as a source of infection after joint replacement surgery [26], avoidance of urinary catheterization is desirable. Although it might be anticipated that the incidence of catheterization would be less in the clonidine group, the results of the present study do not support this, but other factors may have had an influence on the catheterization rate, as patients with a history of urinary symptoms were not excluded from the study.

On the basis of haemoglobin oxygen saturation readings and ventilatory frequency, the results of this study are in agreement with the findings of Bailey and co-workers [27]. They noted that clonidine did not produce respiratory depression when used alone, and its addition to morphine did not increase the risk of respiratory depression.

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EFFECT OF PRE- *VS* POSTOPERATIVE INGUINAL FIELD BLOCK ON POSTOPERATIVE PAIN AFTER HERNIORRHAPHY

G. W. DIERKING, J. B. DAHL, J. KANSTRUP, A. DAHL AND H. KEHLET

SUMMARY

The analgesic effects of an identical inguinal field block, performed before or immediately after inguinal herniorrhaphy, were evaluated in 32 healthy patients in a double-blind, randomized study. During surgery, all patients received a light general anaesthesia with thiopentone, alfentanil and nitrous oxide in oxygen. After inducation of general anaesthesia, patients were allocated randomly to receive an inguinal field block with lignocaine, either 15 min before operation or immediately after operation, after closure of the surgical wound, but before the patients were awake. Pain score on a visual analogue scale and on a verbal scale at rest, during mobilization from supine into sitting position and during cough was assessed 1, 2, 4, 6, 8 and 24 h, and 7 days after operation. No significant differences between the groups were observed in VAS scores or verbal pain scores during rest or ambulation at any time. There was no significant difference in time to first request for morphine or total morphine consumption. These results do not show pre-emptive analgesia with a conventional inguinal field block to be of clinical importance compared with a similar block administered after operation.

KEY WORDS

Anaesthetic techniques, regional: inguinal block. Pain: postoperative.

Experimental studies have demonstrated that peripheral tissue injury may lead to long lasting alterations in central processing, with reduction in threshold, amplification of responses, expanded receptive fields and afterdischarges of dorsal horn neurones [1, 2]. Furthermore, innocuous inputs may begin to generate pain [1–3]. Subsequently, it has been suggested that surgical trauma in humans may lead to comparable alterations, resulting in amplification and prolongation of postoperative pain [1,2,4].

In experimental studies, central sensitization may be eliminated or reduced if the afferent barrage is prevented from reaching the CNS by preinjury neural block with local anaesthetics [5,6]. This finding, if confirmed in humans, may suggest that changes in the timing of treatment (e.g. pre-emptive neural block) may have profound effects on postoperative pain [1,2,4,7]. However, clinical studies investigating the analgesic effect of pre- *vs* postoperative neural block, and thus the significance of "timing" [1], have not been undertaken. The aim of this study was to compare the effects of the same neural block, performed either before or immediately after surgery, on postoperative pain after inguinal herniorrhaphy.

MATERIALS AND METHODS

We studied 32 healthy patients undergoing unilateral elective inguinal herniorrhaphy in this double-blind, randomized design. Patients with a history of drug or alcohol abuse, chronical pain, regular medication with NSAID or opioids, more than 30% overweight, and those undergoing re-operation were excluded. Informed consent was obtained from all patients, and the study was approved by the local Ethics Committee. The patients received diazepam 10–15 mg by mouth 1 h before operation as premedication. General anaesthesia was induced with thiopentone 3–5 mg kg^{-1}, atropine 0.3–0.5 mg and alfentanil 10 µg kg^{-1}; after administration of alcuronium 2.5 mg, suxamethonium 1.5 mg kg^{-1} was given to facilitate orotracheal intubation. General anaesthesia was maintained with alfentanil 5 µg kg^{-1}/15 min and 66% nitrous oxide in oxygen. Alcuronium 0.3 mg kg^{-1} was used to maintain neuromuscular block.

After induction of general anaesthesia, patients were allocated randomly (closed envelope) to receive an identical inguinal field block either 15 min before operation or immediately after operation, after closure of the surgical wound but before the patients were awake. The technique for local anaesthesia was as follows [8]: From a point 1 cm medial to the anterior superior iliac spine, a needle was inserted perpendicular to the skin until contact with bone was established. Five millilitre of 1% lignocaine with adrenaline was injected during retraction of the needle to skin level. From the same point of injection, 0.5% lignocaine 20 ml with adrenaline was injected

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TABLE I. *Patient data (median (range)). ns = not significant*

	Preoperative block	Postoperative block	*P*
n	16	16	
Age (yr)	46 (25–69)	41 (19–62)	ns
Sex (M/F)	14/2	16/0	ns
Height (cm)	174 (158–185)	180 (170–192)	0.04
Weight (kg)	75 (55–92)	78 (57–93)	ns
Duration of surgery (min)	40 (20–70)	48 (25–90)	ns
Peroperative alfentanil ($\mu g\ kg^{-1}\ min^{-1}$)	0.5 (0.4–1.4)	0.6 (0.4–1.0)	ns

under the aponeurosis of the external oblique muscle, and 0.5 % lignocaine 20 ml with adrenaline was injected s.c., both in a fan-wise fashion in the medio–caudal direction, covering the surgical field; 1 % lignocaine 5 ml with adrenaline was injected directly at the pubic tubercle and finally, 1 % lignocaine 5 ml with adrenaline was injected into the inguinal canal from a point between the anterior superior iliac spine and the pubic tubercle.

All blocks were performed by the same anaesthetist (A.D.), experienced in the use of the technique in patients having surgery in local anaesthesia only. This investigator had no contact with the patients in the postoperative period, and the patients were unaware of the timing of the block. The surgical procedure was performed *ad modum Bassini* in all patients.

After operation, neuromuscular block was antagonized with glycopyrronium 0.5 mg–neostigmine 2.5 mg. All patients were transferred to the same intensive care unit and observed by recovery ward nursing staff experienced in postoperative pain treatment and blinded to the treatment groups. Every 30 min, until 2 h after operation, patients were asked if they needed analgesia. If the answer was yes, morphine 0.1 mg kg^{-1} was given i.v. Patients were then transferred to the general ward, and morphine 0.125 mg kg^{-1} was administered i.m. if requested by the patient. No other analgesics (including paracetamol, aspirin or NSAID) were administered.

Pain scores on a visual analogue scale (VAS) (0 mm = no pain; 100 mm = worst pain imaginable) and on a verbal scale (0 = no pain, 1 = discomfort in the wound but no pain, 2 = mild pain, 3 = moderate pain, 4 = severe pain, 5 = unbearable pain) at rest, during mobilization from supine to sitting position and during cough were assessed 1, 2, 4, 6, 8 and 24 h after surgery, by an investigator blinded to the treatment groups. Patients were instructed in the use of VAS and contacted, by phone, 7 days after operation. They were then interviewed about their pain as described above.

Data are presented as median values and ranges. Visual analogue and verbal pain scores were compared as the sum of the respective scores of each patient from the first 1 h after operation to the 7th day after operation [9]. Tests were made also for each of the points of measurement. Statistical analysis was performed with the Mann–Whitney rank sum test for unpaired data and Fisher's exact test. $P < 0.05$ was considered statistically significant.

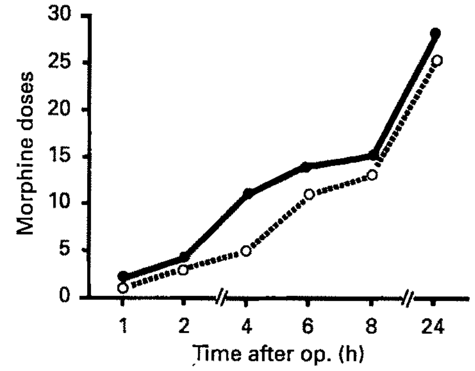

FIG. 1. Cumulative doses of morphine 0.1 mg kg^{-1} i.v. 0–2 h and 0.125 mg kg^{-1} i.m. 2–24 h after inguinal herniorrhaphy. —— = Preoperative inguinal field block ($n = 16$); ----- = postoperative inguinal field block ($n = 16$). ($P = 0.13$).

RESULTS

Sixteen patients received preoperative and 16 patients postoperative inguinal field block. Patient data, duration of surgery and peroperative consumption of alfentanil are shown in table I. Except for body height, there were no significant differences observed between groups.

Time from the end of surgery to the first request for morphine was not statistically significantly different between the preoperative block (pre.) group (median 240 min (range 30–∞)) and the postoperative block (post.) group (360 min (60–∞)) ($P = 0.31$). Four patients in the pre. group and three patients in the post. group received morphine during the first 2 h after operation. Two patients in the pre. group and three patients in the post. group did not receive morphine during the first 24 h after operation. Cumulative morphine requirement in this period was not statistically significantly different between groups (fig. 1) ($P = 0.13$).

No significant differences between groups were found in VAS scores (fig. 2) or verbal pain scores (fig. 3) at rest, during mobilization from the supine to the sitting position or during cough at any time of measurement, or when compared as the sum of patient score from 1 h to 7 days after operation.

Patients were discharged from hospital a median of 2 days (range 1–4 days) and 1.5 (1–5) days after operation in the pre. and post. groups, respectively ($P = 0.95$).

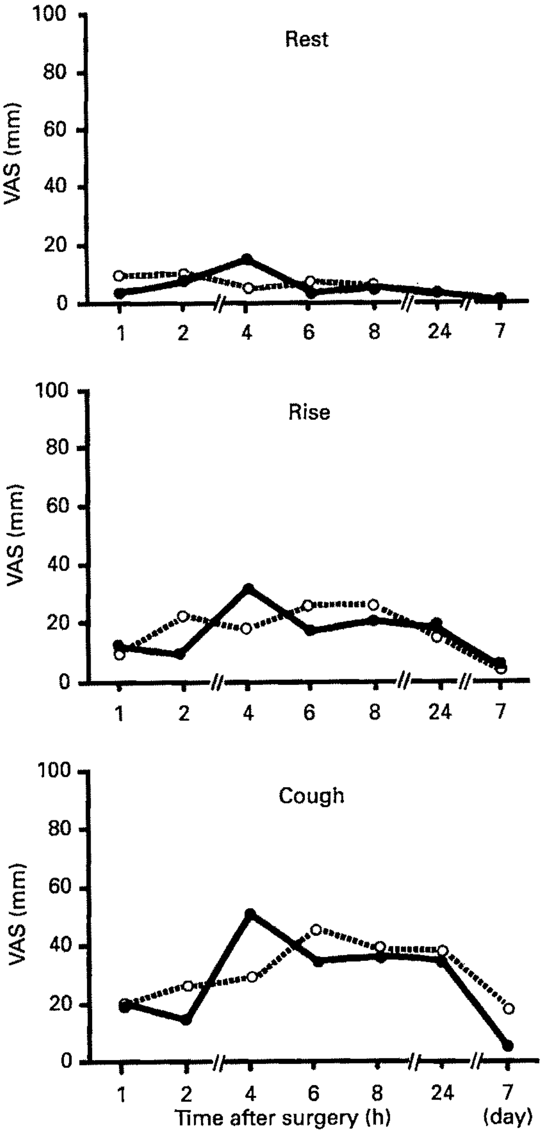

FIG. 2. Median visual analogue scores (VAS) from 1 h to 7 days after inguinal herniorrhaphy in patients at rest (Rest; $P = 0.95$), during mobilization from supine to sitting (Rise; $P = 0.52$) and during coughing (Cough; $P = 0.86$). —— = Preoperative inguinal field block ($n = 16$); ---- = postoperative inguinal field block ($n = 16$).

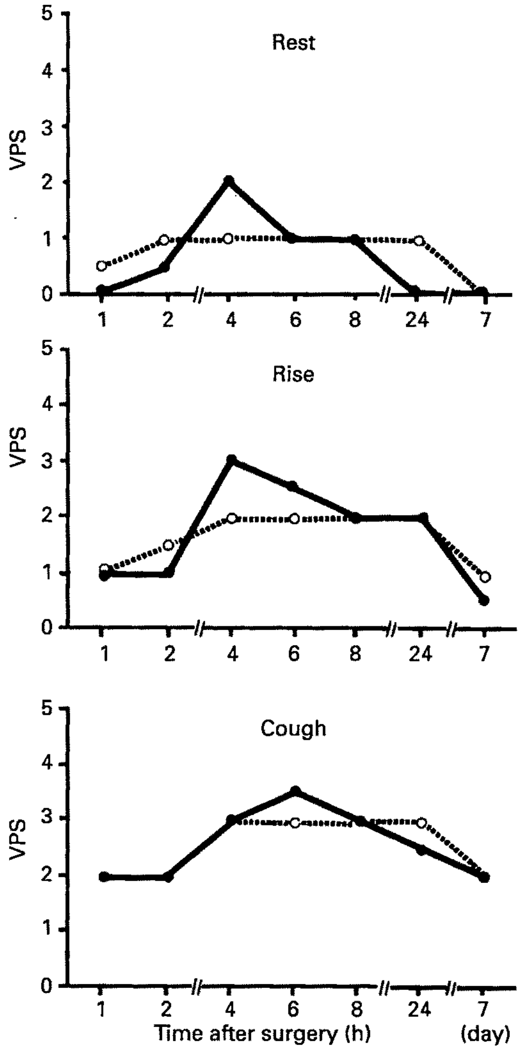

FIG. 3. Median verbal pain scores (VPS) from 1 h to 7 days after inguinal herniorrhaphy in patients at rest (Rest; $P = 0.92$), during mobilization from supine to sitting (Rise; $P = 0.75$) and during coughing (Cough; $P = 0.86$). —— = Preoperative inguinal field block ($n = 16$); ---- = postoperative inguinal field block ($n = 16$).

DISCUSSION

We have found no significant differences in morphine requirements or pain scores between patients with a local anaesthetic field block performed before compared with those in whom block was performed after inguinal herniorrhaphy. A trend, however, was observed towards a longer duration of analgesia in patients receiving postoperative block. This was demonstrated by a median 2-h increase in time to first request for analgesic, corresponding roughly with the difference in time when pre- and postoperative blocks were performed.

The lack of difference in pain scores in our study cannot be attributed to differences in consumption of additional analgesic, as patients in both treatment groups received the same amount of morphine, both in the first 2 h after operation and 24 h after operation.

In a recent study, preoperative incisional neural block before inguinal herniorrhaphy was shown to reduce late postoperative pain and wound tenderness compared with patients operated under general anaesthesia only, while patients receiving preoperative spinal anaesthesia had an intermediate analgesic response [10]. In another study, preoperative spinal anaesthesia and percutaneous ilioinguinal and iliohypogastric nerve block reduced postoperative pain for 48 h after herniorrhaphy compared with patients operated under spinal anaesthesia alone [11]. However, the findings of our study can not confirm previous suggestions [10, 11] that the effect of preoperative block with local anaesthetics on postoperative pain may be a consequence of the initial anaesthetic effect rather than an extended pharmacological action. One explanation of these discrepances may be an extended analgesic effect by local anaesthetic wound infiltration as a result of its anti-inflammatory effect in the study by Tverskoy and colleagues [10]. Furthermore, that study did not examine the influence of pre- compared with postoperative block. The study by Bugedo and colleagues [11] also did not examine the influence of pre- compared with postoperative block; furthermore, their data are difficult to interpret because their patients received various types of postoperative analgesic treatment and pain was examined only at rest [11]. Our study compared only pre- with postoperative block and we cannot argue against previous suggestions that a preoperative [10–14] or postoperative [15–17] administration of local anaesthetics (nerve blocks or infiltration) may have a prolonged effect on postoperative pain compared with systemic analgesic treatment.

The concept of "pain prevention" with local anaesthetics is based on the assumption that pain caused by tissue damage may be a consequence of dysfunction of the central nervous system, with an alteration in the way in which information from the periphery is handled [3]. Experimental studies have demonstrated that localized, peripheral tissue injury (thermal, chemical) or brief afferent C-fibre conditioning stimuli result in increased excitability and expansion of the cutaneous receptive fields of flexor motoneurones and dorsal horn neurones [18,19]. Comparable changes have been demonstrated in other studies [20–23]. Central hyperexcitability may be prevented by local anaesthetics administered before injury [5,6], thus preventing nociceptive signals from gaining access to the central nervous system. It is unclear, however, if the hyperexcitability is driven by peripheral inputs or if it is an independent central neuronal phenomenon. Thus a postinjury local anaesthetic block at the site of injury either abolished [24,25] or had no effect [5,6,18] on central neuronal responses. Only a few clinical studies have investigated the effect of surgery on nociceptive processing in humans [26–28], and most of these studies have failed to demonstrate any pain-induced decrease in somatosensory thresholds. In a recent study, however, allodynia and hyperalgesia to noxious sural nerve stimulation were observed in patients after gynaecological surgery [29], in accordance with experimental observations.

There may be several explanations for the discrepancy between our findings and observations in recent experimental and clinical studies. Although central sensitization may contribute to postoperative pain in humans, surgical trauma differs from the conditioning stimuli applied in experimental studies in several aspects. Contrary to a well-localized thermal or chemical injury, or brief C-afferent stimulation, the afferent input to the CNS during surgery is extensive, with a mixed cutaneous, muscular and visceral component. It is difficult to achieve complete afferent block, even with extradural or spinal anaesthesia [30]. In our study, we investigated the effect of a combination of wound infiltration and peripheral neural block with lignocaine. Both wound infiltration [10,17] and block of the ilioinguinal nerve [10,31] are moderately effective as methods for postoperative analgesia, but do not provide total pain relief, and only the combination is effective for surgical pain [32]. Furthermore, with the combination, both primary hyperalgesia at the wound site and afferent transmission of nociceptive impulses through peripheral nerves may be attenuated. However, as our patients received general anaesthesia in addition to local anaesthesia, we cannot exclude that the pre- or the postoperative afferent block was incomplete; both groups of patients had pain, although moderate, in the early postoperative period. Thus central sensitization may have been induced in both groups of patients as a result of insufficient afferent block.

In surgical patients, it may be postulated that C-afferent activity may be generated not only during surgery, but also in the postoperative period, partly as a result of persistent inflammation and hyperalgesia at the wound site. This activity may be sufficient to produce central sensitization, and no information is available on the optimal duration of afferent block to prevent alterations in dorsal horn neurones after tissue injury greater than that studied in experimental studies [4–6, 18–25]. Lignocaine, as used in our study, is known to have a shorter duration of action than bupivacaine used in previous studies [10,11] and central sensitization may have been induced in both groups of patients, when the pharmacological action of lignocaine had disappeared.

In conclusion, no significant difference in immediate or late postoperative pain was observed between patients who had received an identical inguinal field block either before or immediately after herniorrhaphy. Further studies are needed to compare the effects of neural blocks of different intensity and duration, to clarify the clinical significance of pre-emptive analgesia on postoperative pain. In this context, high-dose extradural analgesia [33], continuous spinal or combined spinal and extradural analgesia [34] may be of interest. Furthermore, the combination of different analgesics ("balanced analgesia" [35]) may have important implications in "pre-emptive analgesia".

ACKNOWLEDGEMENT

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EFFECT OF PHYSIOTHERAPY ON THE AUDITORY EVOKED RESPONSE OF PARALYSED, SEDATED PATIENTS IN THE INTENSIVE CARE UNIT

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SUMMARY

Auditory evoked response (AER) was recorded before, during and after physiotherapy in 11 paralysed (atracurium 0.56 (SD) 0.13 mg kg^{-1} h^{-1}), sedated (propofol 2.2 (1.0) mg kg^{-1} h^{-1}; fentanyl 4.4 (2.3) µg kg^{-1} h^{-1}) and critically ill patients undergoing ventilation in the intensive care unit (ICU). The latency of the negative wave, N_B, was reduced by physiotherapy (mean 44.8 (SD) 7.9 ms before, 41.0 (6.8) ms during ($P < 0.01$, non-parametric Friedman test) and 45.6 (6.3) ms after physiotherapy); N_B amplitude showed no consistent change (−0.81 (1.4) µV, −0.81 (1.5) µV and −0.71 (1.3) µV, respectively). N_B latency responded to patient arousal at constant levels of sedation and this requires further evaluation as a means of monitoring sedation in paralysed patients in the ICU.

KEY WORDS

Brain: auditory evoked response. Intensive care: sedation. Lung: physiotherapy. Monitoring: evoked response.

Inhalation and i.v. anaesthetic agents have been shown to produce dose related changes in the early cortical components of the auditory evoked response (AER) [1, 2]. Anaesthesia-induced changes in the AER are greatest in the easily recognized N_B wave [3]. Surgical incision was associated with an increase in N_B amplitude when end-tidal halothane concentration was kept constant and this has been cited as evidence that the early cortical AER is an index of anaesthetic depth [4]. Thornton and colleagues have proposed that an N_B latency of less than 44.5 ms may be indicative of conscious awareness, even though there may be no subsequent recall [3].

Most patients undergoing controlled ventilation in the Intensive Care Unit (ICU) are sedated and many are also paralysed. Evaluation of depth of sedation is important in order to prevent excessive drug treatment whilst at the same time minimizing patient distress. Sedation scoring is useful, but cannot be applied to paralysed patients who may also show diminished or absent responses to potent stimuli such as tracheal suction.

The aim of this study was to evaluate the practicality of AER monitoring in the Intensive Care Unit and to determine if a relatively standardized form of stimulation (physiotherapy) would cause measurable changes in AER.

SUBJECTS AND METHODS

The study and its consent procedures were approved by the District Ethics Committee. Critically ill patients cannot give informed consent, so we sought the agreement of relatives and proceeded after obtaining this. We studied critically ill patients who required controlled ventilation in the ICU and who were paralysed with an infusion of atracurium and sedated with infusions of fentanyl and propofol. None of the patients was known to have any pre-existing hearing defect. Sedation was stable (constant infusion rates and no clinical change) for at least 2 h before the start of the study and no additional bolus doses were given before physiotherapy. Physiotherapy followed a standardized format and comprised "bag squeezing" (manual hyperinflation of the chest), percussion and shaking of the chest and passive movements of upper and lower limbs. Using a "Navigator" system (Bio-Logic System Corp., U.S.A.) binaural rarefaction click stimuli of 75 dB were given through Telephonics headphones at 6 Hz. AER was recorded using forehead and mastoid silver disc electrodes with electrode impedances of 5 kΩ or less. For each AER, 1500 sweeps were averaged using the following data: high pass filter, 30 Hz; low pass filter, 500 Hz; window, 5–160 ms; 512 points per sweep; amplifier gain 150000. After collection the AER were smoothed using a 13-point running average and the major negative deflection (N_B) of the early cortical AER was analysed in terms of amplitude (µV) and latency (ms). A pilot study demonstrated that it was possible to obtain satisfactory AER from normal subjects in the ICU environment using this equipment. Consecutive pairs of AER were collected before, during and after physiotherapy.

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TABLE I. *Patient data, drug treatment and outcomes for the 11 patients according to outcome (mean (range or* SD))

	All patients	Returned to ward	Died on ICU
n	11	6	5
Age (yr)	45.2 (24–75)	41.3 (31–69)	49.8 (24–75)
Sex (M/F)	6/5	3/3	3/2
Weight (kg)	75.7 (7.6)	72.7 (8.9)	79.4 (5.3)
Propofol (mg kg^{-1} h^{-1})	2.2 (1)	2.1 (1)	2.3 (1.1)
Fentanyl (µg kg^{-1} h^{-1})	4.4 (2.3)	3.3 (1.4)	5.7 (2.8)
Atracurium (mg kg^{-1} h^{-1})	0.56 (0.13)	0.50 (0.13)	0.63 (0.089)
Primary diagnosis		Renal transplant failure Respiratory failure Septicaemia Respiratory failure Acute asthma Multiple injuries	Perforated duodenal ulcer Respiratory failure Leukaemia + cytomegalovirus Pancreatic fistula After cardiac arrest

TABLE II. *Haemodynamic and AER data for the 11 patients according to outcome (mean* (SD)). *Significant changes:* *$P < 0.05$; **$P < 0.01$ *(non-parametric Friedman test)*

	Before physiotherapy	During physiotherapy	After physiotherapy
All patients ($n = 11$)			
Systolic arterial pressure (mm Hg)	111 (17.2)	124 (22.4)*	114 (14.7)
Mean arterial pressure (mm Hg)	78 (14.5)	82.9 (17.1)	78.4 (12.9)
Diastolic arterial pressure (mm Hg)	61 (14.8)	62 (16.1)	61 (13.0)
Heart rate (beat min^{-1})	90 (26.1)	92 (26.7)	88 (24.3)
N_B latency (ms)	44.8 (7.9)	41.0 (6.8)**	45.6 (6.3)
N_B amplitude (mV)	−0.81 (1.4)	−0.81 (1.5)	−0.71 (1.3)
Returned to ward ($n = 6$)			
Systolic arterial pressure (mm Hg)	114 (19.9)	127 (27.8)	118 (16.4)
Mean arterial pressure (mm Hg)	82 (16.9)	89 (21.1)	83 (14.9)
Diastolic arterial pressure (mm Hg)	67 (17.4)	69 (18.8)	66 (14.2)
Heart rate (beat min^{-1})	97 (28.3)	98 (28.0)	93 (27.8)
N_B latency (ms)	45.7 (8.7)	40.1 (6.3)	45.8 (6.1)
N_B amplitude (mV)	−1.16 (0.2)	−1.31 (0.59)	−0.92 (0.3)
Died in the ICU ($n = 5$)			
Systolic arterial pressure (mm Hg)	107 (14.6)	120 (16.1)	110 (12.5)
Mean arterial pressure (mm Hg)	72 (10.3)	76 (8.5)	72 (7.2)
Diastolic arterial pressure (mm Hg)	55 (8.9)	54 (7.0)	54 (7.5)
Heart rate (beat min^{-1})	82 (23.6)	86 (26.0)	81 (20.4)
N_B latency (ms)	43.7 (7.8)	42.2 (7.9)	45.2 (7.2)
N_B amplitude (mV)	−0.39 (2.0)	−0.21 (2.1)	−0.45 (2.0)

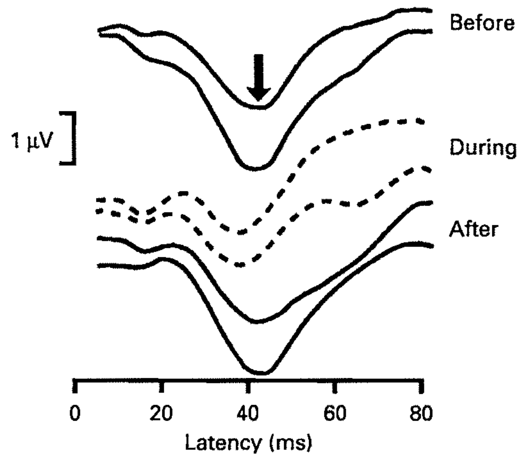

FIG. 1. Six consecutive recordings (redrawn) of the early and middle cortical components of the auditory evoked response from a single patient before, during and after physiotherapy. The window (5–160 ms) and filtering (high pass 30 Hz, low pass 500 Hz) result in the brain stem response not being shown. During physiotherapy the latency of the N_B wave (arrow) decreased.

Values for the left and right sides were averaged together, as were the pairs of AER obtained in each of the three conditions; before, during and after physiotherapy.

Arterial pressure was recorded from an arterial line (radial or brachial) using a calibrated manometer system (Spacelabs, U.S.A.).

Data were analysed using the non-parametric Friedman test. The package Statview II (version 1.03) was run on an Apple Macintosh computer.

RESULTS

Data were obtained from 11 patients, of whom five died in the ICU and six returned to the general ward. Patient data, diagnoses, drug treatments and outcomes are listed in table I.

We obtained satisfactory AER recordings in the ICU, although careful positioning of equipment was necessary to minimize mains interference. With careful attention to electrode placement and removal of avoidable sources of mains interference, we were able to make satisfactory recordings in all patients selected for the study. Unlike previous studies of

AER in anaesthetized patients, it was not possible to make control recordings in the awake state. The AER of sedated ICU patients is relatively flattened and the only early cortical wave which could be identified confidently in all patients was the negative wave N_B. N_B latency was reduced significantly by physiotherapy ($P < 0.01$, non-parametric Friedman test), whereas N_B amplitude was not affected consistently, increasing in some patients and decreasing in others (fig. 1, table II).

When the data were reanalysed according to patient outcome (table II), differences between survivors and non-survivors became apparent. The N_B latency decreased markedly during physiotherapy in survivors, whilst those patients who died showed a smaller response.

DISCUSSION

We set out to recreate the definitive experiment of Thornton and colleagues [3] with appropriate modification for the ICU setting. We have demonstrated that the AER of patients in a "steady state" of paralysis and sedation on the ICU does show a reversible response to physiotherapy. Although we believe that the shortening of the N_B latency which we observed was caused by cortical arousal provoked by physiotherapy, it is important to consider other possible explanations. Physiotherapy may cause profound, short lived changes in arterial blood-gas tensions and in haemodynamic state, and the possibility exists that we have witnessed an epiphenomenon of such changes. Bag squeezing with 100% oxygen increases Pa_{O_2} and may have some effect upon Pa_{CO_2} (depending upon the fresh gas flow and the amount of rebreathing which occurs). Notwithstanding this, the changes we have observed are consistent with other observations that arousal can reduce N_B latency [3].

The N_B latencies we have measured were less than the 44.5 ms threshold of awareness [3] or became so during physiotherapy. If we extrapolate principles derived from patients studied during anaesthesia into the ICU setting, the implication is that many of our paralysed and sedated patients are in a state of conscious awareness, even if they have no recall in the event that they recover. This study did not set out to evaluate AER as an outcome predictor, and the number of patients studied is too small to draw conclusions on this subject; nevertheless, it is interesting that the group of patients who survived showed a greater reduction of N_B latency in response to physiotherapy than did those who died. The patients who died received more sedation than those who did not and this could have contributed to the difference, although the additional amounts of propofol and fentanyl were relatively small.

We studied each patient for a single period on one day only; repeated measurements are certainly possible, but the inconvenience of the additional equipment and the difficulty of maintaining good electrode placement may make this impractical.

We conclude that AER measurement is feasible on critically ill patients in the intensive care unit and that its use should be evaluated further. Further work could usefully investigate the sensitivity and specificity of this response, or some variant of it, as an outcome predictor.

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DOES A SUBPARALYSING DOSE OF VECURONIUM ENHANCE DIAPHRAGM FATIGUE?

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AND P. DUVALDESTIN

SUMMARY

We have examined, in six healthy volunteers, the effect of a subparalysing dose of vecuronium on the development of diaphragm fatigue. Vecuronium was given as a 0.5-mg bolus i.v. followed by 0.5 mg infused over 30 min; as a control, saline was given in random order. Diaphragm strength was assessed by measuring transdiaphragm pressure and by electromyography. Diaphragm fatigue was induced by breathing against an inspiratory resistance. The plasma concentration of vecuronium varied between 15 and 30 ng ml^{-1} 15 min after administration of vecuronium was started. Peripheral neuromuscular block was not detected in any subject. Diaphragm fatigue developed within the same period in both groups: mean 334 (SD 166) s after saline and 345 (190) s after vecuronium. The electromyographic pattern of diaphragm fatigue and the time constant of relaxation of transdiaphragm pressure after fatigue were similar in both groups. We conclude that, at low plasma concentrations of vecuronium, similar to those present in the postoperative period, there was no predisposition to diaphragm fatigue.

KEY WORDS

Neuromuscular relaxants: vecuronium, subparalysing dose. Ventilation: diaphragm fatigue.

A fraction of postsynaptic receptors of the neuromuscular junction may be occupied by a neuromuscular blocking agent without clinical sign of neuromuscular blocking effect, provided the fraction of receptors occupied is within the safety margin [1]. However, the safety margin varies according to the mode of nerve stimulation: the greater the frequency, the narrower is the safety margin [2]. During maximal contractions, there is an increase in the firing rate of motor neurones [3]. A small residual concentration of neuromuscular blocking drug may not affect muscle strength at rest, but may favour development of muscular fatigue. For respiratory muscles, Gal and Golberg observed that low doses of tubocurarine did not alter quiet breathing, but impaired maximal inspiratory capacity [4]. During recovery from anaesthesia, work of breathing may increase because of upper airway obstruction or shivering, and it is questionable if a residual concentration of blocker may hasten development of diaphragm fatigue. In order to test this hypothesis, we have evaluated the effect of a low dose of vecuronium on diaphragm strength and endurance.

SUBJECTS AND METHODS

Assessment of diaphragm strength

We studied six healthy male volunteers, aged 25–45 yr, with the approval of our local Clinical Investigation Committee. All subjects were seated during the study.

Diaphragm strength was assessed by measuring the transdiaphragm pressure (Pdi)—the difference between abdominal (Pga) and pleural pressure (Ppl). Pga and Ppl were measured using two balloon catheter systems connected by polyethylene tubing to the two ports of a differential pressure transducer (Validyne DP 15). One balloon, filled with 0.5 ml of air, was positioned in the middle one-third of the oesophagus [5] to measure changes in pleural pressure; the second, filled with 1 ml of air, was positioned in the stomach to determine changes in gastric pressure. Pdi was recorded during voluntary contractions produced by sniffing ($P\mathrm{di}_{\mathrm{sniff}}$) [6]. Subjects were instructed to make the sniff short and sharp, to achieve but not sustain peak $P\mathrm{di}_{\mathrm{sniff}}$, as indicated on an oscilloscope. The $P\mathrm{di}_{\mathrm{sniff}}$ curve was analysed in two ways: peak $P\mathrm{di}_{\mathrm{sniff}}$ value was measured and considered an index of maximal diaphragm strength, and the time constant of diaphragm relaxation, τ, was calculated from the later position of the Pdi decay curve [6] by plotting the pressure signal on a logarithmic scale [6]. This yielded a straight line over the 50–70 % lower part of the curve. The time constant τ of this exponential position is equal to the reciprocal of the slope of this line [6].

Electrical muscle activity (EMG) of the diaphragm was recorded by an oesophageal electrode [7], from which the myoelectric potentials were passed to a Disa 15 G01 differential amplifier with band-pass filtering of 10–1000 Hz. The signal from the amp-

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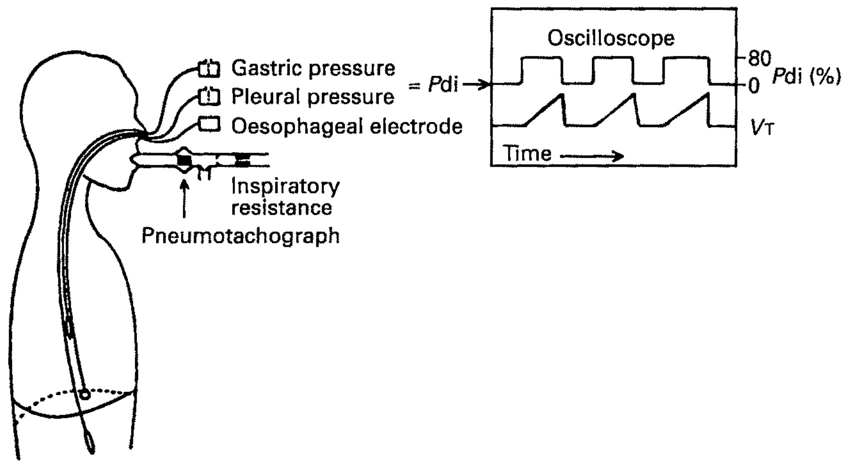

FIG. 1. Experimental design. Subjects inspired through resistance to be able to produce a predetermined transdiaphragm pressure (Pdi). Pdi was measured with two balloons as the difference between gastric and oesophageal pressure (expressed as % of Pdi_{sniff}), and displayed on an oscilloscope, together with tidal volume. EMG of the diaphragm was measured by an oesophageal electrode.

lifier was recorded simultaneously on a magnetic tape for further analysis. The signal from the tape was passed subsequently through two band-pass filters with ranges of 20–46 Hz for the lower frequency component (L) and 150–350 Hz for the high frequency component (H) [8]. The filtered signals were rectified and integrated and the results displayed on a paper recorder.

Assessment of diaphragm endurance

For the diaphragm endurance test, subjects breathed through a Hans-Rudolf valve with the inspiratory inlet connected to a variable resistance. The inspiratory resistance was adjusted so that the subject could achieve a Pdi equal to 80% of the predetermined Pdi_{sniff}. Pdi was displayed on an oscilloscope marked with the target pressure that the subject had to sustain for 2 s (fig. 1). Expiration was performed without added resistance. Ventilatory frequency was set at 12 b.p.m. and tidal volume at 0.75 litre. The endurance test was continued until the diaphragm fatigued, as defined by failure to sustain 80% Pdi_{sniff} for three or more consecutive breaths. Diaphragm EMG activity was recorded continuously throughout the endurance test. The amplitudes of the H and L signals were measured in arbitrary units, and the mean H:L ratio during three consecutive breaths was taken to give a single value for this time span. The H:L ratio was calculated at the 5th, 10th, 15th, 20th and 30th breaths of the endurance test.

Monitoring of peripheral neuromuscular transmission

The ulnar nerve was stimulated at the wrist (Grass S 88) via surface electrodes, using train-of-four stimuli delivered every 12 s throughout the study. The elicited strength of the adductor pollicis muscle was measured by a force displacement transducer (Statham UC3). The train-of-four ratio (T4:T1) was monitored continuously.

Experimental procedure

After a period of 2 days of training, the subjects were studied on two days separated by 1 week. Vecuronium or saline was given to each subject in a random order. Vecuronium 0.5 mg was given as a bolus, followed by a continuous infusion of vecuronium of 0.5 mg given over 30 min. To avoid diplopia after administration of vecuronium, subjects were blindfolded during the first 10 min.

A venous blood sample (15 ml) was obtained from the antecubital vein of the contralateral arm before and 15 min after the start of the i.v. administration of vecuronium or saline, for measurement of plasma concentration of vecuronium in triplicate, in 2-ml samples using the Rose Bengale fluorimetric method [9]. The smallest detectable concentration of vecuronium was 10 ng ml^{-1} in a 2-ml plasma sample. A first set of Pdi_{sniff} values was obtained 10 min after the start of administration of vecuronium or saline (t1), then diaphragm endurance was assessed. A second set of Pdi_{sniff} measurements was made within 15–30 s after the end of the endurance test (t2).

Results are given as mean (SD). Comparisons between group data were evaluated by paired t test. The H:L ratio during the endurance test was compared using repeated measures analysis of variance. For all tests, $P \leqslant 0.05$ was considered significant.

RESULTS

No change in the elicited single twitch response or in T4:T1 ratio was observed throughout the study. Pdi_{sniff} and τ did not differ significantly after administration of vecuronium or saline (table I). Therefore, the target Pdi of the endurance test (80% Pdi_{sniff}) was set at the same value for both groups.

The duration of diaphragmatic endurance was 334 (166) s after saline and was virtually unchanged after vecuronium: 345 (190) s (fig. 2). After the endurance test, peak Pdi_{sniff} was significantly smaller ($P < 0.05$), and τ significantly greater ($P < 0.05$) than at t1 after either vecuronium or saline, indicating that the diaphragm was fatigued in both groups. Pdi_{sniff} and τ did not differ significantly between the groups at t2.

Because the individual variation in the daily H:L ratio derived from EMG measurements was large,

TABLE I. *Mean values* (SD) *of transdiaphragm pressure during sniff test* (Pdi_{sniff}) *and time constant of relaxation* (τ) *before* (*t1*) *and after* (*t2*) *diaphragm endurance test in the saline and vecuronium groups. Significant difference* ($P < 0.05$) *between t1 and t2 values for all variables*

	Pdi_{sniff} (cm H_2O)		τ	
	Saline	Vecuronium	Saline	Vecuronium
t1	115 (29)	110 (22)	90 (13)	86 (9)
t2	96 (30)	95 (25)	102 (17)	96 (11)

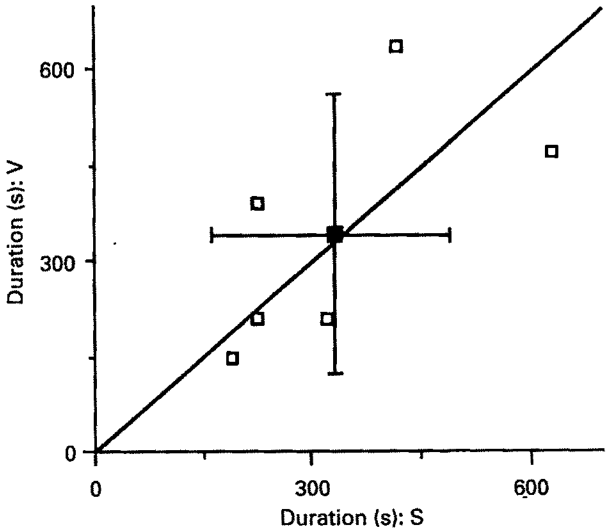

FIG. 2. Individual (□) and mean (■ (SD)) changes in endurance test duration after saline (S) and vecuronium (V) in the six subjects. Solid line = line of identity.

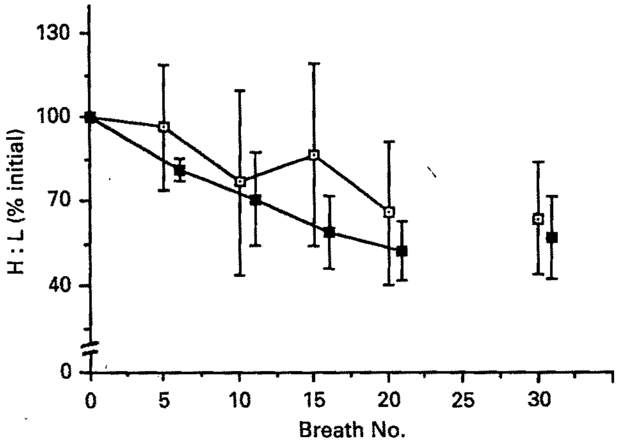

FIG. 3. Mean (SD) value of H:L ratio of diaphragm for all subjects as a function of breath number after saline (□) and vecuronium (■). Each point is the average of three inspirations.

we averaged the H:L ratios of the first three breaths of each run, and assigned to the average a value of 100%, using the method of Gross and colleagues [8]. The H:L ratios of the subsequent breaths were calculated as a percentage of this value. The mean changes in H:L ratio with time during the endurance test are shown in figure 3. There was a systematic decrease in H:L ratio after the first few breaths. No significant difference in the H:L ratio was noticed between saline and vecuronium throughout the endurance test.

Vecuronium was detectable in the plasma of all subjects 15 min after the start of vecuronium administration in concentrations of 15 ng ml^{-1} (two subjects), 20 ng ml^{-1} (two) and 30 ng ml^{-1} (two).

DISCUSSION

The conditions produced in the present study are consistent with those usually found after spontaneous recovery from neuromuscular block. There was no sign of a neuromuscular blocking effect detectable by the usual methods of monitoring: there was no decrease in the elicited twitch response and no train-of-four fade, throughout the study. By comparing the changes in plasma concentration of vecuronium reported in other studies [10, 11] with our observations, we estimate that, after administration of vecuronium 0.1 mg kg^{-1}, a plasma concentration of vecuronium 15 ng ml^{-1} is present within 90–200 min, and a concentration of 30 ng ml^{-1} within 70–150 min. In comparison, the spontaneous recovery to 100% twitch tension has been shown to occur at 74 min after vecuronium 0.1 mg kg^{-1} [12]. Thus our study conditions approximately reproduced clinical conditions found up to 30 min after complete spontaneous recovery from vecuronium-induced block.

Several mechanisms may cause postoperative respiratory failure, including the residual depressant effect of anaesthetic agents on respiration, pulmonary regurgitation, pulmonary atelectasis, postoperative pneumothorax and respiratory muscle fatigue [13]. Diaphragm fatigue could be caused by impaired response of the muscle to excitation (contractile fatigue), by impaired neural or neuromuscular transmission (transmission fatigue), or both [3]. Diaphragm fatigue may occur more easily under circumstances when the muscle is weak, as during curarization. Gal and Golberg [4] demonstrated that administration of tubocurarine 0.15 mg kg^{-1} in normal subjects produced a 37% decrease in maximum *P*di, which for a given work of breathing increases the ratio of *P*di to maximum *P*di, leading to earlier diaphragm fatigue [13]. However, diaphragm muscle impairment in this situation is associated with important clinical signs of peripheral block, inability to sustain a head lift for 5 s, and marked reduction of the train-of-four ratio of the adductor pollicis muscle in response to ulnar nerve stimulation. Because the dose of vecuronium we administered did not reduce maximal *P*di generation, it is unlikely that this agent favoured development of contractile fatigue.

Although transmission fatigue has been questioned in normal man [3], failure of electrical neuromuscular transmission accompanies the loss of force that occurs during sustained maximal voluntary contraction of the adductor pollicis [14]. This phenomenon has been reported also in a rat model when diaphragm fatigue was induced by repeated phrenic nerve stimulation [15]; transmission fatigue contributes markedly to the fatigue induced by brief high-frequency stimulation, and prolongs that caused by low-frequency stimulation [3]. Neuromuscular blocking agents, even in small plasma concentrations, produce subclinical changes in neuromuscular transmission which may favour development of diaphragm fatigue. Although diaphragm muscle has a greater margin of safety than peripheral muscle [16], neuromuscular impairment may occur earlier when a sufficient number of receptors are blocked, while this muscle [15] is submitted to a high and sustained activation. Physiological muscle activation is tetanic, and tetanic fade corresponds to a lesser occupancy of postsynaptic receptors by non-depolarizing agents than does train-of-four fade [17, 18]. In our study, neither train-of-four ratio nor Pdi_{sniff} was altered after administration of vecuronium. However, had sufficient diaphragm neuromuscular receptors been blocked by administration of a small dose of vecuronium, transmission fatigue may have been more likely to develop, especially with large values of *P*di [3].

Our finding that diaphragm fatigue developed similarly after administration of saline or vecuronium indicates that subclinical plasma concentrations of vecuronium do not impair diaphragm function or enhance diaphragm fatiguability.

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RECOVERY FROM DAY-CASE ANAESTHESIA: COMPARISON OF TOTAL I.V. ANAESTHESIA USING PROPOFOL WITH AN INHALATION TECHNIQUE

J. J. NIGHTINGALE AND I. H. LEWIS

SUMMARY

A prospective, double-blind study was conducted to compare postoperative recovery after either total i.v. anaesthesia (TIVA: propofol and alfentanil) or an inhalation technique (propofol and alfentanil followed by nitrous oxide and isoflurane) in 50 patients undergoing day-case gynaecological surgery. Psychomotor performance was assessed at 1 and 2 h after surgery using the Critical Flicker Fusion Threshold (CFFT), Simple Reaction Time (SRT) and Choice Reaction Time (CRT). Subjective recovery and side effects after discharge from hospital were assessed using a postal questionnaire. Recovery occurred significantly earlier in the TIVA group as assessed by CFFT and SRT ($P < 0.01$); there were no significant differences ($P > 0.05$) between the two groups in CRT, subjective duration of recovery or side effects.

KEY WORDS

Anaesthetic techniques: inhalation, total i.v. anaesthesia. Recovery: psychomotor performance. Surgery: day-case.

Patients undergoing outpatient surgery require an anaesthetic technique which allows rapid recovery and discharge from hospital. Barbiturates, benzodiazepines, antidepressants and general anaesthetic agents depress psychomotor performance in normal human subjects [1, 2]. Propofol is redistributed rapidly and metabolized to pharmacologically inactive metabolites [3]. Psychomotor performance recovers earlier after propofol anaesthesia compared with methohexitone used either as a single dose for dental procedures [4] or in incremental doses to supplement regional anaesthesia [5]. Psychomotor recovery occurs earlier also after incremental propofol and nitrous oxide compared with isoflurane and nitrous oxide used to maintain anaesthesia for short gynaecological procedures [6]. There are no previous studies comparing postoperative psychomotor performance in patients receiving either inhalation or total i.v. anaesthesia.

The present study was designed to compare postoperative recovery after either total i.v. anaesthesia (TIVA) or an inhalation technique (IT) in patients undergoing outpatient gynaecological surgery. Critical Flicker Fusion Threshold (CFFT), Simple Reaction Time (SRT) and Choice Reaction Time (CRT) were used to assess postoperative psychomotor performance; a patient questionnaire was used to assess recovery and side effects after the patient's discharge from hospital.

PATIENTS AND METHODS

The study was approved by the local Ethics Committee. We studied 50 female patients (aged 16–60 yr, ASA I or II) undergoing dilatation and curettage. Women undergoing surgery for termination of pregnancy were excluded. Written consent was obtained from each subject. Subjects were allocated randomly to either the TIVA group or the IT group. Restricted randomization was used to ensure equal numbers in each group [7]. Individual patients were allocated by the investigator administering the anaesthetic (I.H.L.). All patients were unpremedicated and none was taking psychoactive drugs before surgery.

In both groups, anaesthesia was induced using i.v. alfentanil 0.5 mg and propofol 2 mg kg^{-1}; patients in the IT group initially breathed 67% nitrous oxide and up to 3% isoflurane in oxygen. Both groups of patients breathed spontaneously via a mask and Mapleson A circuit. Anaesthesia was maintained sufficient for surgery by use of 10-mg increments of propofol with 100% oxygen in the TIVA group, and 67% nitrous oxide plus 1–2% isoflurane in oxygen in the IT group. Signs of inadequate anaesthesia included spontaneous movement, resistance to leg elevation during positioning of the patient, an increase in heart rate and arterial pressure or an increase in the rate or depth of ventilation. Monitoring during anaesthesia included electrocardiography, non-invasive arterial pressure and pulse oximetry. Paracetamol was prescribed for postoperative analgesia and domperidone for postoperative nausea and vomiting.

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TABLE I. *Format of postal questionnaire*

Thank you for participating in this investigation today. We would be grateful if you could answer the following questions and return the form using the stamped addressed envelope provided.

In the first 72 hours (3 days) after leaving hospital did you suffer from any of the following
(Please circle *one* YES or NO):

1. NAUSEA?	YES NO
2. VOMITING?	YES NO
3. HEADACHE?	YES NO
4. DROWSINESS?	YES NO
5. ANY OTHER SIDE EFFECTS?	YES NO

If you answered YES to number 5. please give details in the space below:

Finally AT WHAT TIME DID YOU FEEL COMPLETELY RECOVERED FROM THE ANAESTHETIC? Please give the DATE, TIME, AFTERNOON or MORNING?

Thank you for your help.

CFFT, SRT and CRT were assessed in each patient by the second, blinded investigator (J.J.N.) on three occasions during the study (before operation, as a baseline; and at 1 h and 2 h after surgery) using the Leeds Psychomotor Tester [8] and the method of testing described by Narang and Laycock [9]. CFFT has been defined as the frequency at which a flickering light causes a subjective sensation of a steady light [2]. The assessment of SRT and CRT used six-choice response buttons arranged in an arc. SRT measures a simple motor response to an expected visual stimulus; CRT is based on a choice of responses and measures both sensori-motor performance and attentional ability [1]. Depression of psychomotor performance results in a reduction in CFFT and an increase in SRT and CRT.

Each patient was given a questionnaire (table I) to determine the incidence of side effects in the first 72 h after surgery. Patients were asked also to record when they felt completely well, in order to calculate subjective recovery time (taken from the end of surgery to the time of feeling completely well).

Data are presented as mean and SD. Results were analysed using the unpaired *t* test and ANOVA (Analysis of Variance) for continuous variables; chi-square test with Yates' correction or Fisher's exact test (if the smallest of expected numbers was < 5) were used to analyse discrete variables [7]. $P < 0.05$ was considered statistically significant.

RESULTS

The duration of anaesthesia (taken from the start of induction to the end of surgery) was significantly longer ($P = 0.04$) in the IT group (table II). The dose of alfentanil at induction (0.5 mg kg^{-1}), although unrelated to weight, was comparable to a dose of 7.5 µg kg^{-1} used by Heath, Ogg and Gilks [10] in a similar study. The mean total dose of propofol used in the TIVA group was 240 mg (2 mg kg^{-1} at induction followed by 0.2 mg kg^{-1} min^{-1} as increments). This was similar to the infusion rates of 10 mg kg^{-1} h^{-1} used by Gunawardene and White [11] and 12–15 mg kg^{-1} h^{-1} used by Price and colleagues [12].

TABLE II. *Patient and operative data (mean [range] (SD)). *Significant difference (P = 0.04) between the two groups (unpaired t test)*

	TIVA group (*n* = 25)	IT group (*n* = 25)
Age (yr)	37.2 [20–54]	40.4 [25–52]
Weight (kg)	68.1 (12.6)	63.4 (9.6)
	[50–88]	[53–77]
Duration of anaesthesia and surgery (min)	7.9 (2.7) [4–13]	9.6 (3.0)* [5–15]

TABLE III. *CFFT, SRT and CRT (mean(SD)). Significant differences from baseline (ANOVA): **P < 0.01; ***P = 0.001*

	TIVA group (*n* = 25)	IT group (*n* = 25)
CFFT (Hz)		
Preop. baseline	30.3 (2.5)	28.7 (2.9)
1 h after surgery	27.9 (2.0)***	26.3 (2.9)***
2 h after surgery	29.2 (2.1)	27.3 (3.0)**
SRT (ms)		
Preop. baseline	404 (60)	430 (93)
1 h after surgery	423 (70)	501 (176)**
2 h after surgery	386 (56)	454 (105)
CRT (ms)		
Preop. baseline	628 (97)	691 (156)
1 h after surgery	687 (124)**	832 (275)**
2 h after surgery	627 (105)	734 (162)

TABLE IV. *Incidence of postoperative side effects and subjective recovery time after discharge from hospital. No significant difference between the two groups (P > 0.05 (Fisher's exact, chi-square or unpaired t test) for all effects)*

	TIVA group (*n* = 21)	IT group (*n* = 18)
Headache (No. (%))	4 (19)	6 (33)
Drowsiness (No. (%))	10 (48)	7 (39)
Nausea or vomiting (No. (%))	1 (5)	3 (17)
Other side effects (No. (%))	5 (24)	4 (22)
Recovery time (h (range))	17 (1–72)	12 (1–24)

CFFT was significantly smaller 1 h after surgery compared with baseline in both groups; at 2 h, CFFT in the TIVA group did not differ significantly from baseline, whereas CFFT remained significantly smaller in the IT group (table III). SRT remained unchanged compared with baseline at 1 h and 2 h after surgery in the TIVA group, but in the IT group there was a significant increase in the SRT at 1 h compared with baseline. At 2 h after surgery there was no difference. CRT in both groups was significantly greater 1 h after surgery compared with baseline. In the TIVA group, CRT returned to the baseline value 2 h after operation; in the IT group a small increase was observed at 2 h ($P = 0.07$).

Thirty-nine patients (78%) completed postoperative questionnaires. There were no significant differences in the incidences of headache, drowsiness and emetic symptoms; other minor symptoms (weakness, flushes and backache) occurred in fewer than 25% of patients in both groups (table IV). There was a large range in the reported subjective recovery times for both groups; patients in the IT group felt completely recovered earlier than patients in the TIVA group (table IV), although this difference was not significant ($P = 0.18$).

DISCUSSION

We have found significant differences in two of three psychomotor performance tests during recovery from a total i.v. anaesthetic technique (propofol and alfentanil) compared with an inhalation technique (propofol and alfentanil for induction followed by nitrous oxide and isoflurane). Recovery was more rapid in the TIVA group, as assessed by CFFT and SRT. Nightingale and Norman [13] found CFFT to be a sensitive index of psychomotor performance after general anaesthesia; the present study confirms this finding and suggests, furthermore, that CFFT and SRT are more sensitive indices of postoperative psychomotor recovery than CRT. The significantly greater duration of anaesthesia and surgery for the IT groups is to be expected because of the greater length of time required to establish surgical anaesthesia using volatile agents; this has been observed in a previous study [6].

The advantages of TIVA compared with IT include reduction in the potential for administration of hypoxic gas mixtures, less environmental pollution and absence of exposure of patients and staff to nitrous oxide and volatile agents. Low flow absorption breathing systems have been recommended to reduce atmospheric pollution [14]; however, the economies and reduced emission inherent in the circle breathing system cannot be exploited for short surgical procedures because of the initial high fresh gas flows required to achieve denitrogenation and uptake of anaesthetic agents [15]. In the present study we used a Mapleson A breathing circuit and the estimated costs of incremental propofol (TIVA group) and isoflurane (IT group) for maintenance of anaesthesia were similar.

Although rapid recovery of postoperative psychomotor performance appears to be an additional advantage of TIVA, the clinical significance of subtle differences in psychomotor recovery may be open to debate. Korttila and Linnoila [16] demonstrated impairment of both psychomotor performance and simulated driving after i.m. diazepam or pethidine in normal subjects. These authors reported also an association between psychomotor performance and real driving behaviour in traffic. All outpatients undergoing surgery should be advised, verbally and in writing, on activities which should be avoided after discharge from hospital. However, a recent Audit Commission report on day surgery [17] found that 20% of patients complained of inadequate information concerning expected postoperative medical problems.

It is interesting to note that there were no differences between the two groups in the incidence of postoperative emetic symptoms; the overall incidence of emesis for both groups was low (10%) in the first 72 h after surgery and no patient experienced emetic symptoms or required an anti-emetic whilst in hospital. Postoperative nausea and vomiting are common in women [18] and dilatation of the cervix may be a predisposing factor [19]. Both nitrous oxide [20] and isoflurane [18] are associated with postoperative emesis, but there is evidence to suggest that propofol may reduce the incidence of postoperative emetic sequelae [21].

The rapid recovery of psychomotor performance after total i.v. anaesthesia seen in this study was not associated with a subjective feeling of complete recovery by the patient during the first 72 h after surgery. Whilst measurable differences in recovery exist between different anaesthetic techniques, the clinical significance of these differences remains questionable.

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HEART RATE PERIODICITIES DURING INDUCTION OF PROPOFOL–NITROUS OXIDE–ISOFLURANE ANAESTHESIA

D. C. GALLETLY, T. CORFIATIS, A. M. WESTENBERG AND B. J. ROBINSON

SUMMARY

This study examined the variation in cardiac interbeat interval during induction of anaesthesia with propofol and subsequent inhalation anaesthesia with nitrous oxide and isoflurane. In comparison with preoperative control values, heart rate variability was reduced by anaesthesia and there was a complex, but consistent, pattern of R–R interval change during induction. Immediately after propofol 2 mg kg^{-1}*, high frequency heart rate oscillations were replaced by low frequency oscillations (0.05 Hz). Subsequently, with decreasing propofol and deepening nitrous oxide–isoflurane anaesthesia, high frequency components returned towards, although not reaching, control values; low and, to a greater extent, mid range (0.1-Hz) frequency components remained reduced. We postulate that these alterations are consistent with an immediate but transient post-induction ventilatory depression, subsequent decrease in efferent sympathetic activity and reduction in baroreflex responsiveness. R–R interval analysis is suggested to be a useful tool in the evaluation of autonomic function during anaesthesia.*

KEY WORDS

Anaesthetic techniques: induction. Anaesthetics, intravenous: propofol. Anaesthetics, volatile: isoflurane. Heart: R–R interval analysis.

The main determinants of heart rate are the sympathetic and parasympathetic efferent input to the atrial sinus pacemaker. Because this autonomic control is the product of complex feedback oscillations within the cardiovascular pressure control system, and because of interacting periodicities caused by ventilation, autonomic activity at the sino–atrial node is changing constantly. In consequence, heart rate shows a marked beat-to-beat variability. Although the full extent of this variability is unlikely to be appreciated from the averaged heart rate values given by standard operating room ECG monitoring systems, it is readily apparent if individual R–R intervals are plotted against time (fig. 1).

In the past 5–10 years, important advances have increased our understanding of heart rate variability (HRV) and its possible clinical applications. Early time domain analyses (measures such as the mean or variance of HRV) have been supplemented by frequency domain analyses by which periodicities within the R–R interval series are examined quantitatively using fast Fourier [1] and autoregressive methods of spectral analysis [2], and the interactions between different physiological variables are examined using transfer function analysis [3]. As a consequence, it has been demonstrated that discrete Fourier spectral components of R–R interval time series reflect different aspects of cardiovascular and autonomic control. At least three spectral components have been identified: two low frequency fluctuations (< 0.15 Hz) reflecting aspects of arterial pressure control and a superimposed high frequency "ventilatory" component in phase with ventilation [4].

During anaesthesia, autonomic function is influenced by the effects of drugs and surgical stimulation in addition to changes in posture, temperature and blood volume. It would seem probable therefore that in addition to the gross alterations in heart rate which are apparent from standard ECG monitoring systems, there may exist more subtle fluctuations in R–R interval variability characteristic of different techniques of anaesthesia and which reflect the changing state of autonomic and cardiorespiratory activity.

In this study we have examined the effects of a standard general anaesthetic technique on the spectral components of R–R interval variability and attempted to explain how such variability may be caused by known autonomic effects of the anaesthetic agents used.

PATIENTS AND METHODS

We studied 10 fasting, unpremedicated ASA I patients (mean age 26.4 yr, range 18–35 yr; three male) undergoing urological or gynaecological surgery under general anaesthesia. None had any evidence of cardiac or respiratory pathology and none was taking regular medications. The study was approved by the regional Ethics Committee and all patients gave written informed consent.

One hour before operation, a continuous 5-min ECG (CM5) recording was made with the subject supine and resting quietly. The voltage output from the ECG monitor (Hewlett–Packard) was passed to a purpose built R wave detector which generated an

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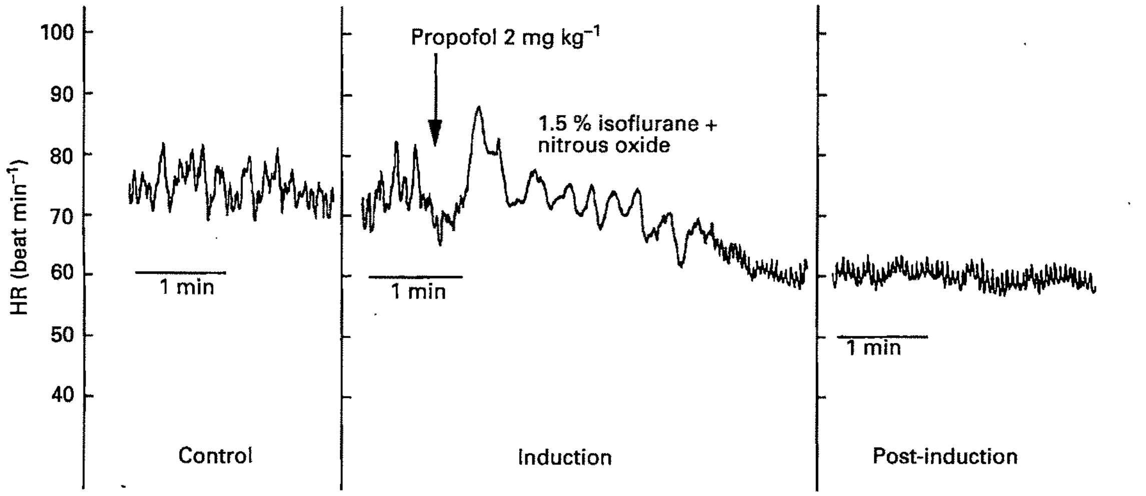

FIG. 1. Heart rate (HR) variability during the preanaesthetic (control), induction and post-induction periods.

accurate 50-ms pulse synchronous with the peak of each R wave. The R wave was detected by half wave rectifying the electronically filtered (high pass to remove P and T waves) and differentiated ECG signal and passing this output to a peak detector which generated the 50-ms pulse when the slope of the signal changed from positive to negative. This pulse was input to the parallel port of a microcomputer (IBM-compatible) which computed the interval between successive R–R intervals and stored these as a series for later analysis.

Anaesthesia was induced with propofol 2 mg kg^{-1} over 15 s into an antecubital vein. A facemask was applied and patients breathed 66 % nitrous oxide and 1.5 % isoflurane in oxygen via a circle absorption system. Transient apnoea was managed, if necessary, by gentle IPPV in order to maintain an oxygen saturation of $> 95\%$. An R–R interval series was recorded throughout the induction sequence and for 15 min after induction, before the onset of surgical stimulation. Episodes of apnoea, IPPV and patient movement were recorded.

Spectral analysis of HRV was performed using a method based on that of Akselrod and colleagues [5, 6]. The raw R–R series were examined for artefacts and any discrete, abnormal intervals caused by ectopic beats were removed using linear interpolation. Artefact-free, stationary segments of 128 s of R–R interval data were then taken from the preoperative recording and from the final minutes of the post-induction recording while patients were breathing nitrous oxide and isoflurane. These segments were sampled at a rate of 4 Hz to produce a series of 512 (4×128 s) discrete values of instantaneous heart rate. This heart rate series was then high pass filtered to remove fluctuations less than 0.015 Hz and low pass filtered at 2 Hz to remove components of greater than Nyquist frequency. A fast Fourier analysis was performed using a Hanning window. The total spectral power (area under the curve) was normalized for the square of the heart rate and the proportion of this power calculated for three frequency ranges, chosen as representative of previously published work [1, 5, 7–9] because individual authors quote slightly different values for each frequency component: low frequency ("vasomotor"), 0.02–0.08 Hz; mid frequency ("baroreflex"), 0.08–0.15 Hz; high frequency ("ventilatory") 0.15–0.45 Hz.

The SD of the instantaneous heart rate series and total power were calculated as a measure of overall HRV.

Differences in spectral power for the three frequency bands were analysed using Student's *t* test for paired data. Differences were considered significant at $P < 0.05$. Analysis was performed using a Statview II statistical package on an Apple Macintosh IIcx microcomputer.

RESULTS

Visual examination of the R–R interval recordings showed a consistent pattern of HRV during the induction sequence. At least three phases were apparent (fig. 1).

(1) Preinduction variability was replaced by a transient smooth acceleration in heart rate. The mean time to onset of this tachycardia was 22 (SEM 1.8) s after the end of propofol injection, with peak heart rate occurring at mean 35 (2.3) s. Heart rate then returned rapidly towards preinduction value.

(2) Over the next approximately 3 min, the most frequent pattern was of a slow heart rate fluctuation. In six patients in whom this periodicity could be measured accurately over five or six peaks, the mean frequency was 0.056 Hz (range 0.049–0.059 Hz).

(3) These low frequency fluctuations in heart rate became less apparent as the high frequency (ventilatory) components returned and increased in amplitude over 5–10 min.

A comparison of spectral components during the resting preoperative period with that 10 min after induction is shown in table I. During anaesthesia, although heart rate was unchanged, heart rate variability decreased. This reduction in HRV was seen as a decrease in total spectral power (-59%) and, to a lesser extent, as a reduction in R–R interval SD (-21%). The power in each of the three frequency bands decreased, although there was a greater reduction in the power of low and more especially the

TABLE I. *Mean* (SEM) *values of HRV data before operation and 10–15 min after the induction of propofol–nitrous oxide–isoflurane anaesthesia. Absolute power is given in arbitrary units. Proportional power is calculated as absolute power for each band divided by total power*

	Pre-anaesthesia	Anaesthesia	Change (%)	*P*
HR (beat min^{-1})	67.20 (2.78)	67.87 (2.29)	+1	ns
HR SD (beat min^{-1})	4.05 (0.94)	3.21 (0.57)	−21	ns
Total power	0.260 (0.058)	0.107 (0.018)	−59	0.02
Low band power	0.049 (0.008)	0.019 (0.002)	−61	0.005
Mid band power	0.055 (0.01)	0.014 (0.002)	−74	0.0018
Low+medium (absolute) power	0.10 (0.02)	0.03 (0.01)	−70	0.002
High band power	0.157 (0.045)	0.073 (0.016)	−53	0.07
Ratio abs. power (Hi (Lo+Med))	1.4 (0.24)	2.1 (0.34)	+50	0.05
Proportion of low band power	0.22 (0.03)	0.217 (0.028)	−1	ns
Proportion of mid band power	0.235 (0.025)	0.134 (0.01)	−43	0.005
Proportion of high band power	0.545 (0.044)	0.648 (0.032)	+19	0.04

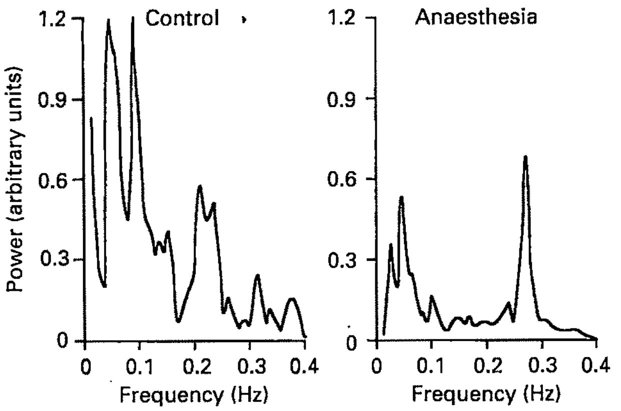

FIG. 2. Power spectrum of heart interval variability during the preoperative period (control) and during nitrous oxide–isoflurane anaesthesia.

mid range frequency components when compared with the high frequency band. The proportion of the total spectral power within the high frequency band increased by 19%, the mid band decreased by 43% and the proportion of the power in the low band was unchanged. During anaesthesia, alteration in the morphology of the high frequency spectral component was apparent also, with the ventilatory peak becoming narrower and more clearly defined (fig. 2). This was considered to reflect a decrease in the variability of ventilatory rhythm during inhalation anaesthesia.

DISCUSSION

We have observed that the recording of R–R interval series during the induction of anaesthesia revealed a complex but consistent pattern of heart rate fluctuations which are presumed to represent the interaction between the changing plasma concentrations of the anaesthetic agents with cardiovascular and ventilatory control mechanisms. Although a comparison of preoperative with intra-anaesthetic R–R interval series showed no significant difference when time domain analysis (heart rate and SD) were performed, differences were revealed clearly using spectral analysis.

In the normal human subject, at least three spectral components of HRV are described [1, 10]:
(1) A low frequency component (centred between 0.04 and 0.08 Hz), is said to represent thermoregulatory fluctuations in vasomotor tone [11] or compensatory baroreflex oscillations in heart rate, for arterial pressure fluctuations at the same frequency, which are caused by peripheral vasomotor variability, and which are normally damped by the renin–angiotensin system [5]. The cardiac efferent component is mediated by parasympathetic and beta-sympathetic activity and may be enhanced (or "undamped") by angiotensin converting enzyme inhibitors [1, 5].
(2) Mid range frequencies centred as 0.12 Hz (the "10-s rhythm" or the Mayer waves of arterial pressure [12]) have been ascribed to the activity of a 10-s brain stem oscillator and modulating effect of the baroreflex or its frequent response [13, 14]. In the supine position, the efferent control is predominantly parasympathetic, while a greater sympathetic component is present with standing or during tilt [10, 15, 16].
(3) High frequency components, in phase with ventilation, are ascribed to oscillating baroreflex responsiveness during breathing [17], a central coupling of respiratory generator and cardiac vagal efferents, a central vagal reflex arc stimulated by pulmonary stretch receptor activation and, since small fluctuations still occur in denervated heart transplants and IPPV, changes in right ventricular preload and myocardial wall stretch [18]. The ventilatory component is thought to be controlled by parasympathetic vagal efferents (the sympathetic nervous system is too sluggish to operate at this high frequency) and, apart from small mechanically mediated fluctuations, is abolished by atropine [15, 16].

Donchin, Feld and Porges [19], examining the effect of isoflurane–nitrous oxide anaesthesia on high frequency (0.12–0.4 Hz) parasympathetic spectral components, observed a diminution of the ventilatory heart rate variability and related this to a reduction in vagal tone. These authors postulated that changes in high frequency variability might be used as a measure of depth of anaesthesia, although subsequent work from Yli-Hankala and colleagues [20] found no relationship between anaesthetic depth and the ventilatory component of HRV for more than 1 MAC of isoflurane and enflurane.

Two major effects of propofol–isoflurane–nitrous oxide anaesthesia on HRV were observed in the present study. First, immediately after induction with propofol, high frequency "ventilatory" fluctuations were almost abolished, being replaced by a low (0.056-Hz) frequency heart rate periodicity. Second, after approximately 3 min, and presumably as the isoflurane–nitrous oxide inhalation anaesthesia deepened and the initial effects of propofol decreased, the fast ventilatory component assumed an increasing dominance over the low and, more especially, the mid range frequencies; however, its absolute power returned only to approximately 50% of the preoperative control value. In comparison with the unanaesthetized state, there was an overall reduction in HRV, seen as a reduction in total spectral power.

The initial acceleration in heart rate after propofol occurred at approximately the same time as the onset of CNS depression and within one arm–brain circulation time. This acceleration may be a result of a parasympathetic, sympathetic or direct sino–atrial node action. Subsequent, low frequency waves at 0.05 Hz (with a period of 18 s) are too fast to be caused by recirculation and therefore are most likely to be the low frequency components of the cardiovascular control system. The dominance of these low frequency waves immediately following propofol could come about through a number of mechanisms. First, it is probable that the "ventilatory" high frequencies are so markedly depressed that normal background low frequency components are unmasked. Such high frequency depression may have been caused by:

(1) A parasympatholytic effect of propofol reducing vagal efferent activity. Although this is supported by animal studies, in which a dose-dependent reduction in the vagal component of the baroreflex arc has been demonstrated [21] and would explain the observed initial tachycardia, in humans such an effect of propofol has not been shown [22]. Furthermore, at times when low frequencies dominate the Fourier spectrum in the period immediately after induction, the heart rate in some patients was little different from preinduction values.

(2) Reduced ventilatory depth or effort after propofol injection. Ventilatory depression is a transient but well described feature of propofol induction. In conscious subjects, a reduction in tidal volume is associated with a reduction in high frequency spectral energy and may, through a complex dynamic interaction, cause a corresponding increase in lower frequency components [18, 23, 24].

(3) Peripheral vascular dilatation or increased capacitance [25–27] from propofol would be expected to reduce venous return and reduce the activity of atrial and arterial stretch receptors. This reduces the parasympathetic dominance of sino–atrial control and thereby reduces the parasympathetic ventilatory component of HRV.

In addition to depression of ventilatory fluctuations, it is also possible that the low frequency waves are increased by a sympathetically mediated response to sudden changes in capacitance induced by propofol [27]. Such an effect is observed in dogs during infusion of nitroglycerine [28] or haemorrhage [29]. These observations might, therefore, be consistent with a peripheral vascular action of propofol [26].

During subsequent isoflurane–nitrous oxide inhalation, the power in all frequency bands was reduced compared with preoperative values. However, as a proportion of total spectral power, high frequency fluctuations dominated over the mid frequencies and, to a lesser extent, over low frequency vasomotor activity. In addition to a return of normal ventilatory depth, the following mechanisms could help explain these changes:

(1) The reduction in low and mid range frequencies during isoflurane anaesthesia might reflect both a relative decrease in adrenergic activity from a preoperative stressed condition and an absolute decrease in normal background sympathetic tone as anaesthesia deepened (isoflurane–nitrous oxide anaesthesia reduces efferent sympathetic activity by 56% at 1.0 MAC [30]).

(2) Low and mid range frequencies are under the control of parasympathetic and sympathetic efferents; a reduction in vagal efferent activity (consistent with the ability of isoflurane to increase heart rate) could help explain the reduced low and mid range power and explain the smaller reduction in absolute power of the high frequency component.

(3) Low and mid range frequency bands are baroreflex mediated. As isoflurane, as with all general anaesthetics, depresses baroreflex activity (30% depression at 1.0 MAC [31]), a corresponding reduction in these spectral components would be expected. Despite their diminution, however, at least one component (0.05-Hz) remains active throughout the induction sequence and subsequent inhalation anaesthesia. This is consistent with other studies which have shown the presence of intact baroreflex sympathetic control under both isoflurane and propofol anaesthesia [21, 30, 32]. Because the baroreflex frequency (0.1 Hz) is depressed to a considerably greater extent than vasomotor fluctuations at 0.05 Hz, it is possible that the inhalation anaesthetic agents or residual effects of the propofol are in some way depressing the source of the "10-s" baroreflex oscillator, while leaving intact the baroreflex mechanism itself.

This preliminary study, examining the brief period of anaesthetic induction and deepening inhalation anaesthesia cannot reveal in detail the mechanisms that underlie the observed complexities of HRV. Under more steady state conditions, however, and with additional recording of ventilation and other cardiovascular indices, it is possible that HRV analysis could be a useful tool in the haemodynamic investigation of anaesthetic drugs. Previous reports on the cardiovascular actions of propofol have shown inconsistent changes for heart rate in the first few minutes after bolus injection [23]. This is explained readily by examining the complex fluctuations in HRV seen in figure 1, by researchers' use of ECG heart rate recorders which average multiple R–R intervals and by the standard research procedure of averaging heart rates from the group of patients under study. Except for the period immediately after injection of propofol, clear differences between pre- and intra-anaesthetic heart rate series (which had the same average heart rate) were apparent only when spectral analysis was performed. Averaged heart rate measurements are, therefore, only an approximation to the underlying complexity of instantaneous heart rate. We therefore suggest that HRV spectral decomposition may be a valuable quantitative tool for the analysis of autonomic fluctuations in awake and anaesthetized patients.

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RESPONSE OF 10 PULSE OXIMETERS TO AN *IN VITRO* TEST SYSTEM

K. J. REYNOLDS, J. T. B. MOYLE, M. K. SYKES AND C. E. W. HAHN

SUMMARY

Pulse oximeters are often used in situations in which severe hypoxaemia may occur. We have developed an in vitro *system to test the accuracy of pulse oximeter calibration. The probe of 10 different oximeters was attached to a model finger in an* in vitro *blood circuit, and pulse oximeter readings* ($\mathrm{Sp}_{\mathrm{O}_2}$) *were compared with multi-wavelength* in vitro *oximeter readings* (So_2) *over a range of* So_2 *values from 50 to 100%. The oximeters tested varied widely in their accuracy and linearity. We conclude that the system can test the accuracy, reproducibility and linearity of response of pulse oximeter readings at low oxyhaemoglobin saturations.*

KEY WORDS

Equipment: pulse oximeters. Measurement techniques: pulse oximetry.

Pulse oximeters determine the oxygen saturation of arterial blood by a non-invasive optical technique. They are calibrated using data obtained by inducing hypoxaemia in healthy adult subjects. This is achieved easily at high saturations, but at saturations less than approximately 75%, the acquisition of data becomes more difficult and possibly unethical. Data are limited, therefore, at these low saturations, and calibration is mainly by extrapolation. As calibration is performed individually by each manufacturer for his own instrument, the data used for calibration have been obtained from several subject population types and sizes. It is likely, therefore, that accuracy differs widely between different instruments, especially at low saturations. This has been confirmed in extensive *in vivo* studies by Severinghaus and colleagues [1, 2].

We have developed an *in vitro* system for testing the performance of pulse oximeters over a wide range of saturations. This study determined the response of a range of different pulse oximeters to the *in vitro* test system.

METHODS

Test system

An *in vitro* test system was designed capable of producing signals similar to those obtained from pulsatile arterial blood in the finger (fig. 1).

Whole blood obtained from adult subjects and anticoagulated with heparin is pumped through the circuit by a computer-controlled peristaltic pump. The desired waveform and pulse rate of blood in the circuit are fed into the microcomputer, and appropriate control pulses are applied to a stepper motor driving the pumphead.

Blood is pumped in pulsatile fashion through a cuvette acting as a model finger (fig. 2) and the probe of the pulse oximeter being tested is positioned across the finger. As it is impossible to construct a model finger reproducing exactly the anatomical features of a real finger, we aimed to keep the design of the cuvette as simple as possible (fig. 2). Blood enters from one end of the finger and flows in a thin

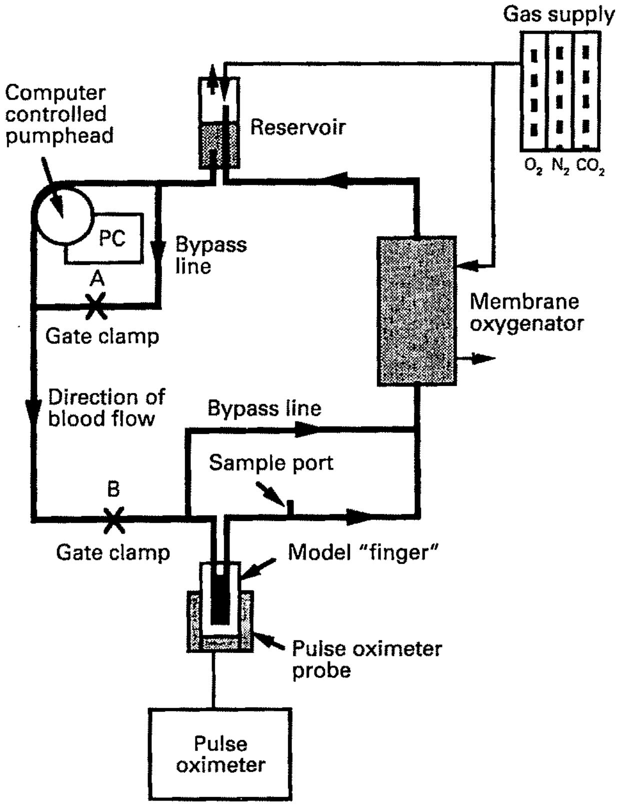

FIG. 1. The pulse oximeter test system.

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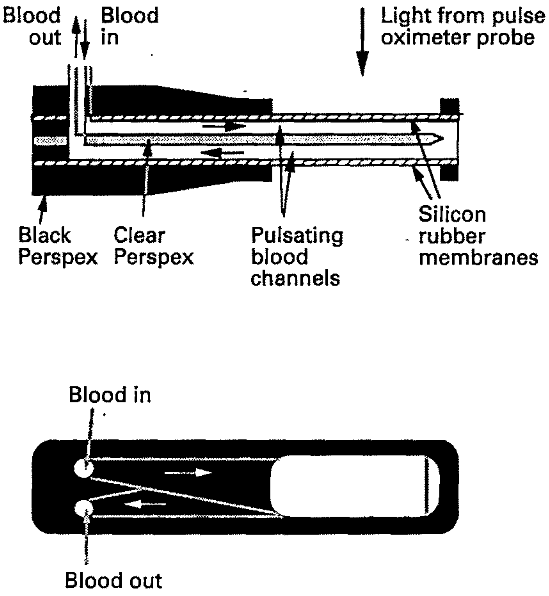

FIG. 2. The model finger used in the test system. Top: side view; below: face view.

(1-mm) layer through the cuvette, over the finger tip end and back in a similar fashion along the underside. Both inlet and outlet are tapered to prevent flow separation. The silicone rubber membranes (0.5 mm thick) allow blood pulsations within the model finger. The a.c.: d.c. signal ratio may be altered by adjusting the gate clamps at points A and B in figure 1. This ratio should be in the physiological range (1:100 to 5:100 [3]).

This design enables flow within the model finger to be developed fully within a short distance from each end of the cuvette, and the pulsations produced in the finger to be consistent along its length. This is necessary because the position of the light sources relative to the "fingertip" end of the oximeter probe varies between makes of oximeter, and so for a valid comparison to be made between different oximeters, the pulsations must be consistent at all positions along the cuvette. A Datex Satlite Versalite (ear) probe was positioned in turn at several places along the length of the cuvette, and the saturation value recorded by the pulse oximeter was found to be repeatable at all positions.

The overall dimensions of the model finger were similar to those of a real finger, to ensure that all oximeter finger probes fitted snugly over the finger. To provide some scattering of the incident light, a piece of translucent draughtsman's paper was inserted between the light sources in the probe and the model finger. This paper, together with the silicon rubber membranes and the red blood cells, causes diffusion of the incident light.

The saturation of blood flowing through the circuit is controlled by a small parallel plate membrane oxygenator. The blood flows between two parallel microporous polypropylene membranes, each with an effective area of 6.4×16.0 cm^2. Nitrogen, oxygen and carbon dioxide pass by diffusion across the membranes.

The composition of the gas mixture passing through the membrane oxygenator is controlled by flowmeters. The percentage of carbon dioxide is maintained at 6 %, while the percentage of oxygen is varied; the balance of the gas mixture is nitrogen.

TABLE I. *Pulse oximeters tested, probe used, data points measured and number of units of blood used*

Pulse oximeter	Type of probe	No. data points	Blood used (units)
Datex Satlite (DA)	Ear	98	12
Nellcor N-200 (NE)	Finger	31	6
Ohmeda Biox 3700 (OH)	Finger	91	11
Physiocontrol Life-stat 1600 (PH)	Ear	42	6
Radiometer OX1 (RA)	Finger	81	7
SiMed S-100 (SI)	Finger	96	9
MiniOX IV (MI)	Finger	82	9
Novametrix 515A (NO)	Finger	55	8
Kontron 7840 (KO)	Finger	83	7
Hewlett-Packard Monitor (HP)	Finger	52	5

Finally, the blood enters a small reservoir which damps the pulse wave completely before it returns to the pump. The blood in the reservoir is exposed to the same mixture of gases as that passing through the membrane oxygenator in order to maintain equilibrium.

Experimental methods

Ten pulse oximeters from different manufacturers (table I) were used to test the *in vitro* system. The probe of each pulse oximeter was placed over the model finger.

Blood in the circuit was desaturated to approximately 50% by passing a mixture of 2% oxygen, 6% carbon dioxide, balance nitrogen, through the membrane oxygenator. When equilibrium was reached and the pulse oximeter reading became stable, measurements displayed by the pulse oximeter (Sp_{O_2}) were compared with blood samples withdrawn simultaneously from a sampling port immediately next to the outlet of the model finger. The oxygen saturation (SO_2) of the blood samples was measured immediately using a co-oximeter (OSM3 Hemoximeter, Radiometer Ltd). The Hemoximeter uses six wavelengths of light to measure SO_2 directly, and is capable, therefore, of distinguishing the abnormal haemoglobins, carboxyhaemoglobin and methaemoglobin.

The concentration of oxygen in the gas mixture was increased in 1% steps, and Sp_{O_2} and SO_2 readings recorded when equilibrium was reached at each saturation.

A least-squares linear regression analysis was performed on the data from each pulse oximeter and the correlation coefficients calculated. As pulse oximeters are generally calibrated from empirical data for saturations greater than approximately 75 % and by extrapolation for values less than 75 %, we decided also to analyse these two data ranges separately.

Another useful method of analysis of the data is by calculation of mean bias, ($Sp_{O_2} - SO_2$), and precision, which is the SD of the bias. Mean bias and precision were calculated for each oximeter over all three data ranges.

TABLE II. *Linear regression analysis of Sp_{O_2} on So_2 for the oximeters tested over the saturation ranges 50–100, 75–100 and 50–75 %. (See table I for details of oximeters.) CI = Confidence interval;* SEE *= standard error of estimate;* n = *number of readings*

Pulse oximeter and probe		So_2 range (%)	*n*	Slope (±95 % CI)	SEE	Intercept	*r*	Bias (mean (SD))
DA	Ear	50–100	98	0.80 (0.04)	2.60	18.5	0.97	2.7 (3.7)
		75–100	50	0.92 (0.09)	1.99	7.5	0.95	1.0 (2.0)
		50–75	48	0.71 (0.12)	2.96	24.7	0.86	5.4 (4.2)
NE	Finger	50–100	31	0.94 (0.09)	3.12	5.0	0.97	0.2 (3.1)
		75–100	19	0.94 (0.26)	3.19	4.6	0.88	−0.5 (3.0)
		50–75	12	1.07 (0.26)	3.08	3.3	0.95	1.4 (2.9)
OH	Finger	50–100	91	0.84 (0.04)	2.56	14.4	0.98	1.8 (3.4)
		75–100	45	0.88 (0.09)	1.87	10.6	0.95	−0.2 (2.0)
		50–75	46	0.82 (0.13)	3.12	15.4	0.88	3.7 (3.3)
PH	Ear	50–100	42	0.95 (0.06)	2.67	7.1	0.98	3.5 (2.7)
		75–100	23	0.82 (0.16)	2.10	18.5	0.92	2.9 (2.2)
		50–75	19	1.08 (0.21)	3.10	−0.8	0.93	4.2 (3.0)
RA	Finger	50–100	81	0.59 (0.03)	2.23	38.5	0.97	7.6 (6.5)
		75–100	41	0.72 (0.06)	1.41	26.6	0.97	2.3 (2.5)
		50–75	40	0.47 (0.11)	2.51	45.9	0.81	13.1 (4.5)
SI	Finger	50–100	96	0.50 (0.04)	2.53	47.8	0.94	10.2 (7.3)
		75–100	48	0.68 (0.08)	2.10	32.5	0.92	4.2 (3.1)
		50–75	48	0.35 (0.11)	2.42	57.9	0.70	16.1 (5.0)
MI	Finger	50–100	82	0.59 (0.04)	2.18	43.3	0.96	11.3 (5.9)
		75–100	41	0.57 (0.07)	1.75	44.4	0.93	6.6 (3.7)
		50–75	41	0.62 (0.13)	2.57	40.7	0.84	16.0 (3.5)
NO	Finger	50–100	55	0.65 (0.04)	1.81	35.5	0.98	9.7 (5.0)
		75–100	27	0.66 (0.08)	1.56	35.0	0.96	5.6 (3.0)
		50–75	28	0.69 (0.13)	2.07	33.3	0.91	13.7 (2.8)
KO	Finger	50–100	83	0.58 (0.04)	2.70	37.0	0.95	6.0 (6.2)
		75–100	40	0.76 (0.10)	2.38	21.5	0.92	0.9 (2.9)
		50–75	43	0.46 (0.12)	2.61	45.0	0.93	10.7 (4.4)
HP	Finger	50–100	52	0.49 (0.04)	1.99	48.1	0.96	9.5 (7.6)
		75–100	26	0.69 (0.05)	0.99	30.0	0.98	3.1 (2.4)
		50–75	26	0.32 (0.10)	1.79	58.7	0.82	15.8 (5.4)

Total haemoglobin concentration (tHb) of the blood was adjusted to 11 ± 2 g %. Data were obtained also using the Datex Satlite for tHb of 8 g % and 14 g %, to see if haemoglobin concentration affected the results.

The SD of haemoximeter readings was estimated by analysing 10 samples from 1 ml of blood in a 1-ml syringe. The syringe was capped and placed in ice between readings to prevent the So_2 changing. The measurements were repeated on two further 1-ml samples of blood.

Several *in vivo* measurements were made on hypoxaemic patients in an attempt to confirm the *in vitro* results. The same pulse oximeters and probes as used for the *in vitro* measurements were placed at random on the fingers of each patient, and Sp_{O_2} values recorded. Simultaneously, an arterial blood sample was obtained from each patient and analysed in the OSM3 Hemoximeter to obtain So_2.

RESULTS

Table I shows the number of data points and number of different units of blood used for each pulse oximeter. In all blood samples, the carboxyhaemoglobin and methaemoglobin concentrations were < 1.5 %. These small concentrations of abnormal haemoglobins should not affect the accuracy of the pulse oximeter readings.

Linear regression, correlation coefficient, mean bias and precision are given in table II for the three saturation ranges 50–100 %, 75–100 % and 50–75 % for each pulse oximeter.

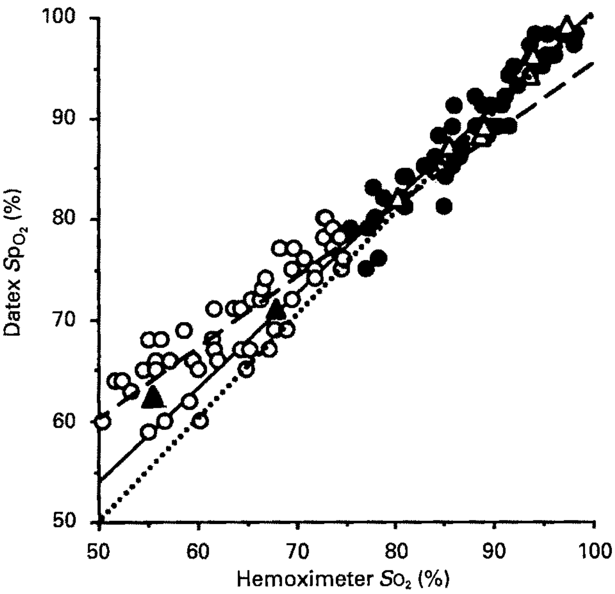

FIG. 3. Comparison between Datex Satlite pulse oximeter readings (Sp_{O_2}) obtained from the test system, and Hemoximeter readings (So_2). Linear regression lines and data points: — ●, data set So_2 > 75 %; —— ○, So_2 < 75 %; ...... indicates identity. *In vivo* data points: △ > 75 %, ▲ < 75 %.

The data points for three makes of oximeter are plotted in figures 3–5, to show the variation in response between different oximeters. *In vivo* results obtained from hypoxic patients are plotted on the same figures to allow comparison with the results obtained from the test system. On each figure, regression lines are drawn for test system data from

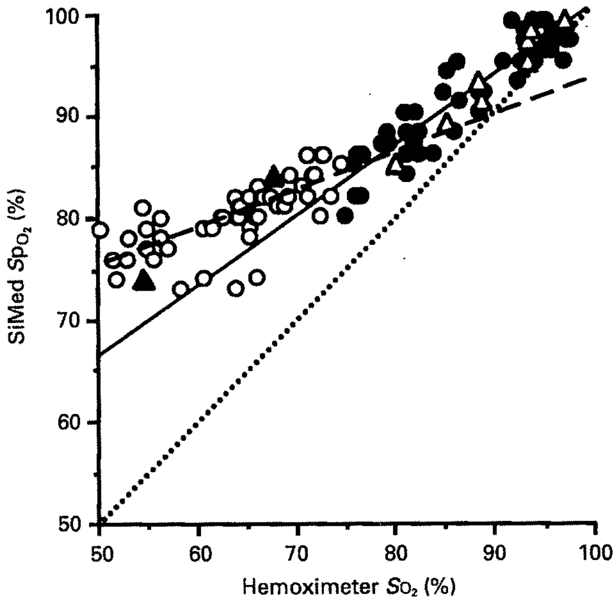

FIG. 4. Comparison between SiMed S-100 pulse oximeter readings (Sp_{O_2}) obtained from the test system, and Hemoximeter readings (So_2). (See figure 3 for explanation of symbols.)

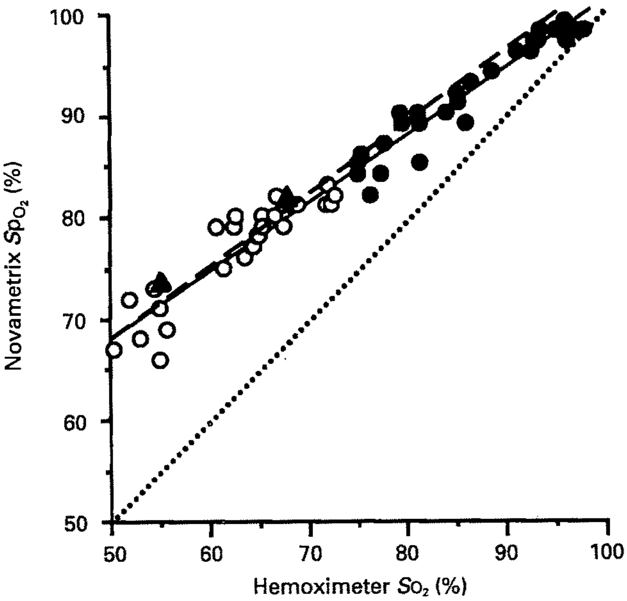

FIG. 5. Comparison between Novametrix 515A pulse oximeter readings (Sp_{O_2}) obtained from the test system, and Hemoximeter readings (So_2). (See figure 3 for explanation of symbols.)

the two saturation ranges 50–75 % (dashed line) and 75–100 % (solid line). These two lines are useful to show the linearity of results between the two data ranges.

All pulse oximeters tended to over-read; this effect was greater at low saturations (table II). The most extreme results were produced by the SiMed (fig. 4) and the HP Monitor, both of which produced readings of approximately 75 % for a true saturation of 50 %.

The correlation coefficient over the entire range measured (50–100 %) was $\geqslant 0.94$ for all instruments. The correlation coefficient over the range 75–100 % for nine of the 10 instruments was $\geqslant 0.92$. Over this range, the Nellcor produced a correlation coefficient of 0.88. This smaller value was attributable to the smaller number of points in the analysis, and one outlying point, rather than to any lesser reproducibility of the results.

Correlation at lesser saturation was less good, with six pulse oximeters producing correlation coefficients of < 0.90 in the 50–75 % range. In all cases (except the Nellcor), the residual variance (or scatter) was greater in the lesser saturation range.

Each pulse oximeter was tested using at least five different units of blood on different days (table I). The results for each oximeter were consistent in repeated sets, which is a necessary requirement for a performance test system.

No significant difference was found between results using the Datex Satlite from blood samples with haemoglobin concentrations of 8 g % and 14 g %. However, scatter of the results can be attributed partly to the SD of So_2 measurement, which was 0.4 %.

DISCUSSION

All the pulse oximeters showed a tendency to over-read at low saturations. This is confirmed by the results of the regression analysis, with regression coefficients for the 50–100 % So_2 range varying between 0.49 for the HP Monitor and 0.95 for the Physiocontrol, and positive values for the mean bias for all pulse oximeters over the range 50–100 %. This tendency to over-read was noticed also by Sidi and colleagues using an Ohmeda Biox 3700 and a Nellcor N-100 on hypoxic dogs [4]. In contrast, *in vivo* measurements made by Severinghaus on healthy adults subjected to profound hypoxia, gave values for regression coefficients between 0.86 and 1.42, and negative biases on several occasions [2].

It was not possible for us to obtain a complete set of *in vivo* results to confirm our *in vitro* results. However, a small number of readings were obtained from hypoxaemic patients with arterial saturations as little as 56 %. These *in vivo* points are plotted with the *in vitro* results for the three oximeters in figures 3–5. The results confirm our *in vitro* results, with all oximeters over-reading to some degree at low saturations. For example, a range of pulse oximeter readings from 69 % (Ohmeda) to 84 % (SiMed) (fig. 4) was obtained from a patient with an arterial saturation of 68.0 %.

As oximeters are calibrated mainly by extrapolation of data at low saturations, calibration in this range is speculative. For this reason, the two ranges greater and less than 75 % were analysed separately. In order to assess the linearity of response of the pulse oximeters, regression coefficients of the entire saturation range (50–100 %), the "calibrated" range (75–100 %), and the "extrapolated" range (50–75 %) were compared, with 95 % confidence intervals for the coefficients (table II). For six of the 10 pulse oximeters, all three coefficients coincided within 95 % confidence limits. Four pulse oximeters, however, (RA, SI, KO, HP) had a significant difference between the regression coefficient in the 75–100 % So_2 range and that in the 50–75 % range. This suggests non-linearity between the calibrated range and the uncalibrated range obtained by extrapolation. An example of this non-linearity of results is shown in figure 4 for the SiMed pulse oximeter. In contrast, results presented in figures 3 and 5 for two other pulse oximeters showed no significant non-linearity.

The increase in scatter at low saturations is in agreement with *in vivo* observations [2, 5]. A possible explanation for this increasing scatter at low saturations may be as follows. The relatively large extinction coefficient of reduced haemoglobin at 660 nm implies that, as saturation decreases, less red light is transmitted through blood, and it appears darker. Any errors in the transmitted light signal at the red wavelength are therefore increased relative to the red signal at low saturations, which leads to a greater variance in Sp_{O_2} at these saturations. Indeed, we found that, if the saturation of the blood in the circuit was reduced to much less than 50%, in some cases the pulse oximeter would register a "noisy signal" warning, suggesting that the errors in the red signal were becoming large relative to the magnitude of the signal itself.

The use of a system such as this may enable manufacturers to reassess and improve the calibration algorithms for their oximeters. However, the results presented in this paper are intended to be used as an assessment of the test system, and should not be extrapolated to a validation of the pulse oximeters themselves, as only one unit from each manufacturer was used. (Severinghaus [2], for example, found large variations between different sets of results using different instruments from the same manufacturer.) Also, the calibration algorithms are continually being updated by the manufacturers, and the oximeters used in our study are not necessarily the latest models and software versions. Kagle and colleagues demonstrated a significant difference between results obtained from an Ohmeda 3700 Version J software and those from the same make of oximeter but containing modified Version XJI software [6].

These studies investigated the use of an *in vitro* system to compare pulse oximeter accuracy. The test system was used under laboratory conditions. Pulse oximeters are known to be affected by a large number of external factors, for example response time [1], accuracy at low perfusion [7, 8], interference by external electromagnetic sources [9, 10] and effect of motion [11]. The test system is potentially able to test the response of pulse oximeters to all these artefacts.

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UPTAKE OF SUFENTANIL, ALFENTANIL AND MORPHINE IN THE LUNGS OF PATIENTS ABOUT TO UNDERGO CORONARY ARTERY SURGERY

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SUMMARY

We have studied the pulmonary extraction and retention of sufentanil, alfentanil and morphine using a double indicator technique in 30 patients undergoing elective aortocoronary bypass surgery. Patients were allocated to three groups (10 each) to receive sufentanil 43 µg, alfentanil 672 µg or morphine 1887 µg, mixed with indocyanine green as indicator. After sufentanil, mean peak extraction was 93.7% (95% confidence interval 87.1–100.4%) and release occurred after 16.1 (13.8–18.4) s; first-pass retention was 61.1 (51.3–70.9)%. After alfentanil, peak extraction was 67.4 (42.7–92.0)% and release occurred after 9.9 (8.5–11.3) s; first-pass retention was 10.1 (3.5–16.7) %. After morphine, peak extraction was 58.3 (44.4–72.2)% and release occurred after 7.2 (4.4–10.1) s; first-pass retention was 7.1 (−4.7–19.9)%. Both peak extraction and first-pass retention were significantly greater after sufentanil. There was no significant difference in the peak extraction and first-pass retention between alfentanil and morphine.

KEY WORDS

Analgesics: alfentanil, morphine, sufentanil. Lungs: pulmonary uptake.

The lungs have important non-respiratory functions, including the elimination, production and excretion of vasoactive substances and conversion of endogenous compounds, for example angiotensin I to angiotensin II [1–4]. Many drugs are subjected also to significant uptake and retention during passage through the lungs [5–7]. For most drugs, uptake and retention are temporary and release occurs as incoming blood concentrations decrease. First-pass retention is significant only for drugs that are both lipophilic and basic; for neutral and acidic drugs, pulmonary first-pass retention is negligible [8,9].

Opioids are basic drugs that, with the exception of morphine, are moderately to highly lipophilic. The pulmonary uptake of morphine is negligible [10], but pethidine, fentanyl and alfentanil undergo significant first-pass retention in the lungs [10–13]. In order to obtain information about the importance of lipid solubility and pK_a, we compared the first-pass pulmonary uptake of sufentanil, alfentanil and morphine—drugs that vary considerably in lipid solubility and pK_a.

PATIENTS AND METHODS

We studied 30 patients undergoing elective aortocoronary bypass surgery. The study was approved by the local medical Ethics Committee and all patients gave informed consent. Patients with unstable angina pectoris, poor left ventricular function as assessed by preoperative angiography, with valvular abnormalities, or with pulmonary disease were excluded. Patients who were taking beta adrenoceptor blocking drugs, calcium entry blocking drugs and nitrates had these medications continued until the morning of surgery. Pulmonary uptake of the drugs was studied in three consecutive groups of 10 patients, in the order alfentanil, sufentanil and morphine.

Patients were given lorazepam 4–6 mg orally 90 min before surgery. All studies were conducted before induction of anaesthesia. In the operating theatre an i.v. cannula and an 18-gauge radial artery catheter were inserted. A pulmonary artery catheter was introduced via the right internal jugular vein.

Indocyanine green 25 mg (Cardio-green, BBL Microbiology Systems, Becton Dickinson) was dissolved in 2.5 ml of solvent and mixed in a plastic syringe with sufentanil 1 ml (50 µg ml^{-1}), alfentanil 1 ml (500 µg ml^{-1}) or morphine 0.2 ml (10 mg ml^{-1}). The volume was made up to 5 ml with autologous blood, which was added to prevent precipitation of the indocyanine green. One millilitre of this mixture was stored for later measurement of the concentrations of indocyanine green and the opioid. The syringe was weighed before and after the bolus injection. The exact doses of indocyanine green and opioid administered were calculated from the injected volume and the measured concentrations.

The remaining opioid–indocyanine green mixture was injected over 1–2 s through the atrial port of the pulmonary artery catheter, followed by a 10-s saline flush. Immediately after the bolus injection, blood sampling commenced. Freely running blood from

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TABLE I. *Patient data, opioid dose and haemodynamics of the three groups (mean (SD)).* $*P < 0.05$

	Sufentanil	Alfentanil	Morphine
No. patients	10	10	10
Height (cm)	174 (9)	169 (7)	172 (6)
Weight (kg)	77.9 (10.0)	77.8 (5.4)	83.3 (7.6)
Body surface area (m^2)	1.91 (0.16)	1.88 (0.09)	1.96 (0.10)
Medications (No. patients)			
Beta blockers	8	7	10
Nitrates	7	8	7
Ca^{2+} entry blockers	4	5	4
Cardiac output (litre min^{-1})	5.34 (1.22)	4.59 (1.07)*	5.99 (0.94)

the radial artery catheter was directed via short extension tubing to a drum, rotating at 1 r.p.m., containing 60 sampling tubes. Each tube contained heparin 40 μl (5000 u ml^{-1}). Individual tubes were exposed to the blood flow for 1 s. Blood sampling was continued until 60 s after injection. From each sample, 0.2 ml was separated for the measurement of indocyanine green concentration, which was performed within 1 h after the experiment. The remaining portion of the whole blood samples was stored at −20 °C until opioid assay.

Indocyanine green concentrations were measured by absorption spectrometry at 805 nm. Sufentanil concentrations were measured by radioimmunoassay, alfentanil concentrations by gas chromatography and morphine concentrations by fluoroimmunoassay. (Details of these assays are described in the Appendix.)

Calculations

Extraction and retention were calculated as described by Geddes and colleagues [5] and Jorfeldt and colleagues [6, 14]. The indocyanine green fraction *vs* time curve was taken as the reference curve representing zero uptake by the lungs. The curve was corrected for recirculation by log-linear extrapolation of the terminal part of the descending portion. The concentrations of indocyanine green and opioids in each sample were expressed as a fraction of the administered dose per millilitre of blood (hereafter referred to as fraction) by dividing the concentration (ng ml^{-1}) by the dose (ng). This fraction was used for further calculation of extraction and retention.

For each sampling time, extraction was calculated by assuming that any difference between the fraction of opioid and the fraction of indocyanine green resulted from retention of the opioid in the lungs. Extraction was calculated as:

$$E^t = \left(1 - \frac{F\text{opioid}^t}{F\textsc{icg}^t}\right) \times 100\,\%$$

where $F\text{opioid}^t$ and $F\textsc{icg}^t$ are the respective fractions of the administered dose per millilitre of blood at sampling time t.

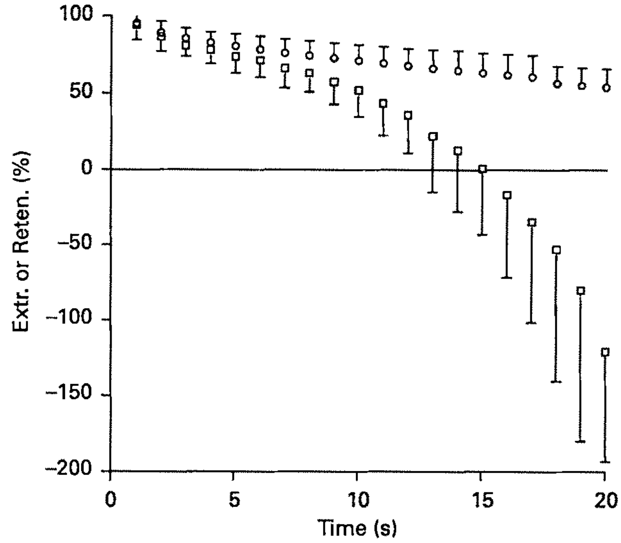

FIG. 1. Mean (SD) pulmonary extraction (Extr.) (□) and retention (Reten.) (○) of sufentanil after rapid i.v. bolus injection of 43.4 (4.9) μg. Time 0 = time of first appearance of indocyanine green at the sample site.

Retention was calculated as:

$$R^t = \left(1 - \frac{\text{AUC}_{0\text{–}t}\text{opioid}}{\text{AUC}_{0\text{–}t}\textsc{icg}}\right) \times 100\,\%$$

where $\text{AUC}_{0\text{–}t}$ is the area under the concentration *vs* time curve up to time t. AUC was calculated by the trapezoidal rule method. First-pass retention was defined as the retention up to the time when 95 % of the total area under the indocyanine green curve was reached. Because possible recirculation of opioid was assumed to have occurred when recirculation of indocyanine green was observed, data from patients in whom recirculation occurred before 95 % of the AUC of indocyanine green was reached were not included in the calculation of extraction and retention. Cardiac output was calculated from the area under the curve and the dose of indocyanine green administered, using the formula:

$$\text{CO} = \frac{D\textsc{icg}}{\text{AUC}\textsc{icg}}$$

Results are expressed as mean (SD) or mean (95 % confidence interval of the mean). Data were analysed using analysis of variance, followed by Newman–Keul's range test when indicated, or χ^2 test. $P < 0.05$ was taken as statistically significant.

RESULTS

Groups were comparable in height, weight, body surface area and preoperative medication (table I). Cardiac output was significantly less in patients in the alfentanil group, compared with those in the other groups.

The administered doses of sufentanil, alfentanil and morphine were 43.4 (4.9) μg, 672 (113) μg and 1887 (769) μg, respectively. In all patients, more than 95 % of the AUC of indocyanine green was reached before recirculation was observed. For all

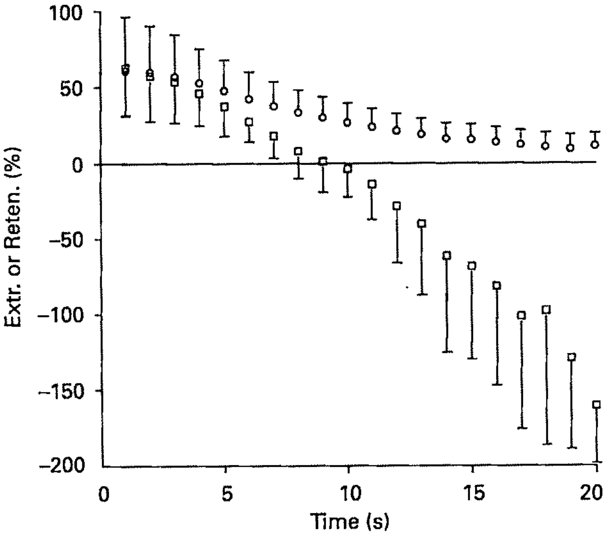

FIG. 2. Mean (SD) pulmonary extraction (Extr.) (□) and retention (Reten.) (○) of alfentanil after rapid i.v. bolus injection of 672 (113) µg. Time 0 = time of first appearance of indocyanine green at the sample site.

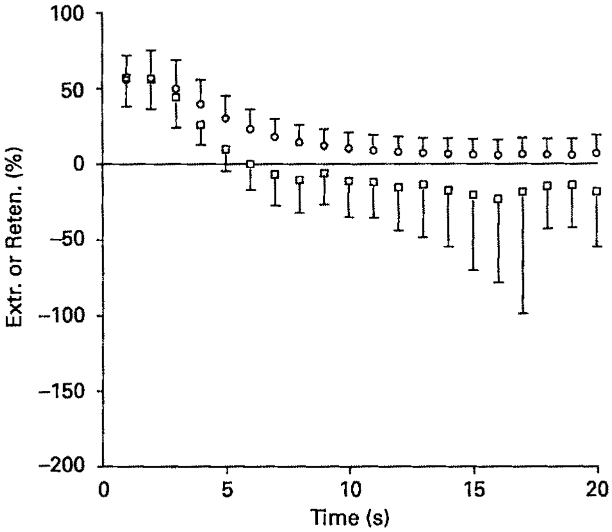

FIG. 3. Mean (SD) pulmonary peak extraction (Extr.) (□) and first-pass retention (Reten.) (○) of morphine after rapid i.v. bolus injection of 1887 (769) µg. Time 0 = time of first appearance of indocyanine green at the sample site.

three drugs, peak extraction occurred within 3 s after the appearance of indocyanine green. Extraction then gradually decreased and after 10–20 s there was net release of opioid from the lungs. The changes in extraction and retention with time for sufentanil, alfentanil and morphine are shown in figures 1–3. The average peak extraction, first-pass retention and the time at which extraction changed to release (pivot point) are shown in table II. In one patient in the morphine group, calculation of the first-pass retention was not possible. In another patient in this group, the pivot point was 32 s after injection, whereas in the remaining nine patients the time to pivot point ranged from 4 to 11 s; the value given for the time to pivot point for morphine in table II is the mean value calculated from these nine patients. The peak extraction and the first-pass retention were significantly greater and the time to the pivot point was significantly longer after sufentanil than after alfentanil or morphine.

DISCUSSION

We have shown that there are marked differences in first-pass pulmonary retention of the opioids sufentanil, alfentanil and morphine. Both the initial extraction and the first-pass retention of sufentanil were significantly greater than those of alfentanil and morphine. The last two drugs were indistinguishable in both peak extraction and first-pass retention.

The pulmonary uptake of morphine in our study was small and comparable to that reported by Roerig and co-workers [10]. The first-pass retention of alfentanil (0–31 %) in our study was less than that reported by Taeger and co-workers [13]. In their study, first-pass retention of alfentanil varied between 35.9 and 79.8 %. Taeger and co-workers studied patients anaesthetized with nitrous oxide and enflurane, receiving intermittent positive pressure ventilation. Our patients were studied during spontaneous ventilation before induction of anaesthesia. It is possible that anaesthesia, positive pressure ventilation, or both, could have contributed to the greater pulmonary retention of alfentanil in the study of Taeger and co-workers.

The first-pass retention of sufentanil found is comparable to that of pethidine (64.5 %), less than that of fentanyl (75.2 %) reported by Roerig and co-workers [10], and comparable to the first-pass retention of fentanyl as reported by Taeger and co-workers, who found values of 43.0–86.9 % [13].

The difference in pulmonary uptake between various opioids may be explained by differences in their physicochemical properties. All opioids are basic drugs, but they differ in lipophilicity, pK_a and protein binding—factors known to influence pulmonary uptake [15–17]. Morphine and sufentanil have similar pK_a values (7.9 and 8.0, respectively), but morphine is highly hydrophilic, whereas sufentanil is highly lipophilic [18]. The difference in lipid solubility may explain the marked difference in

TABLE II. *Peak pulmonary extraction and first-pass retention after bolus injection of three opioids (mean (95 % confidence interval of the mean)). Pivot point = time after first appearance of drug in the arterial blood samples when extraction became zero.* * *P < 0.05.* † *n = 9 (see text)*

	Sufentanil	Alfentanil	Morphine
Peak extraction (%)	93.7(100.4–87.1)*	67.4(42.7–92.0)	58.3(44.4–72.2)
First-pass retention (%)	61.1(51.3–70.9)*	10.1(3.5–16.7)	7.1(−4.7–19.9)†
Pivot point (s)	16.1(13.8–18.4)*	9.9(8.5–11.3)	7.2(4.4–10.1)†

pulmonary uptake between the two drugs. We found that the pulmonary uptake of alfentanil and morphine are similar, although they differ in lipid solubility. Alfentanil is moderately lipid soluble [18], whereas morphine has poor lipid solubility. Pethidine is also moderately lipid soluble [19], but its first pass retention is large and comparable to that of fentanyl [10]. Alfentanil differs from all other opioids in that it has a pK_a (6.5) less than 7.5. It is likely that this is the explanation for the lesser pulmonary uptake of alfentanil. Pulmonary uptake is significant only for basic substances with a pK_a greater than 7.5 [16].

Although protein binding influences the pulmonary uptake of non-basic drugs, it is not a major factor in determining the pulmonary uptake of basic drugs, such as the opioids. In an isolated, perfused rat lung model, the pulmonary uptake of methadone increased only from 40% to 45% when 4.5% bovine serum albumin was omitted from the perfusate [17]. The protein binding of morphine (63%) is less than that of sufentanil (93%), and the lung uptake of morphine is insignificant compared with the latter drug. In contrast, the protein binding of alfentanil and sufentanil are similar [20], but the drugs differ markedly in pulmonary uptake.

All our patients were receiving drugs before surgery, and 25 of 30 patients were taking beta adrenoceptor blocking drugs. Propranolol decreases the pulmonary accumulation of fentanyl both in humans and in an isolated, perfused rat lung preparation [21]. None of our patients was taking propranolol, but it is possible that other beta adrenoceptor blocking drugs similarly affect pulmonary first-pass retention, as these drugs also are basic amines. However, the pulmonary uptake of opioids in the five patients who were not taking beta adrenoceptor blocking drugs was not different from that in other patients in the same group. There is no available information about the influence of other drugs used by our patients, such as calcium entry blockers, on pulmonary uptake of opioids.

The double indicator dilution technique, although easy to use, has the disadvantage that only information on pulmonary uptake over a very short time interval after injection is possible. An alternative approach is to use a mass balance technique. Using this method, Taeger and co-workers [13] showed that the release of fentanyl was described best by a bi-exponential equation with half-lives of 0.22 min and 5.78 min. An important disadvantage of the mass balance technique is that it relies on the assumption that pulmonary blood flow remains constant during the measurement period. This is often difficult to achieve, as many drugs alter the haemodynamic state.

Pulmonary uptake of drugs has clinical implications. For drugs with extensive uptake, the lungs act as a temporary capacitor, reducing peak arterial concentration and thus the risk of side effects whenever a change in pulmonary arterial blood concentration occurs, for example after central venous or peripheral venous bolus injection, or a change in an infusion rate [1]. Pulmonary uptake continues until partitioning between blood and lung tissue is complete, or until the pulmonary arterial blood concentration decreases to less than the equilibrium concentration in lung tissue. Pulmonary uptake of basic lipophilic amines is extensive and saturable. The mean first-pass lung uptake of propranolol was 75% in patients who had not previously taken the drug and 33% in patients receiving regular oral treatment with propranolol [5]. Interactions have been shown also between propranolol and fentanyl [21]. Studies in a rat isolated, perfused lung preparation co-perfused with propranolol and fentanyl demonstrated inhibition of fentanyl uptake by propranolol. In patients not taking propranolol mean (SE) first-pass pulmonary uptake of fentanyl was 86 (1.4)% whereas in a group that had received propranolol 30–120 mg day^{-1} for at least 1 month, first-pass pulmonary uptake of fentanyl was 53 (6.3)%, and in one patient it was only 20.3% [21]. The authors calculated that, in patients receiving chronic propranolol therapy, the decrease in first-pass pulmonary uptake of fentanyl would result in two to four times more of an injected dose entering the systemic circulation in the first 30–60 s after injection.

Compartmental pharmacokinetic models are based on the assumption that, after i.v. bolus injection, a drug is mixed instantaneously and completely within its central compartment. In practice this is never the case. It has been suggested that a pharmacokinetic model that took account of pulmonary uptake would better describe the complexities of early drug distribution and of the dynamics of pharmacological effect [22]. Therefore, early mixing in this central compartment should be distinguished from early drug distribution to the peripheral compartments [23,24].

In conclusion, we have shown that sufentanil undergoes significant first-pass retention in the lungs. The pulmonary retention of alfentanil and morphine was insignificant. Sufentanil is a basic amine, is highly lipophilic and has a pK_a that is greater than 7.5. These physicochemical properties are important for pulmonary retention.

APPENDIX

Indocyanine green measurement

Whole blood 0.2 ml was diluted with distilled water 2 ml and vortexed vigorously to lyse the red cells. The solution was centrifuged for 15 min at 4000 r.p.m. Absorption at 805 nm was measured in the supernatant with an absorption spectrophotometer (Milton Roy type Spectrotronic 301). The mean absorption of the first five to seven samples, in which no indocyanine green was present, was taken as the background absorption and was subtracted from the absorption measured in the remaining samples. The concentration in each sample was calculated from a reference curve, constructed by adding a known amount of indocyanine green to whole blood samples from eight patients. The coefficient of variation was 2.6–3.9% for the relevant range of concentrations.

Sufentanil assay

Whole blood sufentanil concentrations were determined by radioimmunoassay. To 0.3 ml of whole blood, 1 ml of sodium hydroxide 0.1 mol $litre^{-1}$ and n-heptane-isoamyl alcohol 4 ml were added and the solution was mixed for 10 min on a rotary mixer (Protherm type Cenco PT 1510). The solution was centrifuged for 10 min at 4000 r.p.m. (Heraeus Minifuge GL) and the supernatant evaporated to dryness in a stream of dry nitrogen on a water bath at 60 °C. Absolute alcohol 50 µl was added and the solution again vortexed. Bovine serum albumin (Sigma no. A-7888 RIA grade) 450 µl in phosphate buffer (pH 7.5) was added and the tube was vortexed again. Fifty microlitre of the solution was added to 2% bovine serum albumin 450 µl, the mixture vortexed and ^{3}H-sufentanil (Janssen, Beerse, Belgium) added. After further vortexing, antiserum 100 µl (Janssen, Beerse, Belgium) was added. The solution was left at room temperature for 2 h, 500 µl of a Norit–Dextran suspension was added to each test tube and the solution was incubated for 1 h. The solution was centrifuged for 10 min at 4000 r.p.m., 20 °C, decanted into a new test tube and 4 ml of liquid scintillation cocktail (Ultima Gold, Packard) added to the supernatant. Standard solutions, initial binding and antiserum-free samples (to determine non-specific binding) were treated similarly. Scintillation was measured (as d.p.m.) in a liquid scintillation analyser (Packard, Tricarb 2000 CA). The detection limit of this assay was 2 ng ml^{-1} and the average coefficient of variation was 7%. The initial binding was 35% and the coefficient of non-specific binding was 1.4% of total binding.

Alfentanil assay

Whole blood alfentanil concentrations were determined by capillary gas chromatography. To 0.2 ml of whole blood, the internal standard, R 38527 (Janssen Pharmaceutica, Beerse, Belgium), was added and, after vortexing, the sample was extracted for 30 s with 5 ml of redistilled reagent grade n-pentane (Merck, Darmstadt, GFR) on a whirl mixer. After centrifugation, the organic phase was transferred to a conical centrifuge tube and evaporated to dryness in a stream of dry nitrogen on a water bath at 40 °C. The residue was dissolved in analytical grade ethanol 50–100 µl (Merck, Darmstadt, GRF) and 1 µl was introduced into the gas chromatograph via a falling-needle solid injection system (Chrompack, Middelburg, The Netherlands). A Hewlett–Packard 5890A gas chromatograph was equipped with a nitrogen detector and a capillary fused silica column (length 10 m, internal diameter 0.32 mm) with CP-Sil-5-CB (Chrompack, Middelburg, The Netherlands) as the stationary phase. The operating temperatures of the injection port, column oven and detector were 300 °C, 230 °C and 300 °C, respectively. Helium was used as the carrier gas (flow rate 4 ml min^{-1}) and an auxillary flow of helium 26 ml min^{-1} was fed into the detector. Retention times for alfentanil and the internal standard were 1.8 min and 2.6 min, respectively. The detection limit was 1 ng ml^{-1}. The coefficient of variation did not exceed 5% in the concentration range encountered in this study.

Morphine assay

Whole blood morphine concentrations were measured by polarization fluoroimmunoassay—a technique which has become available for the measurement of opioids in whole blood [25,26]. In these studies, correlation of measured morphine concentrations with spiked whole blood calibration curves was 0.999 and the coefficient of variation in these studies was in the range 4.7–12%. We used this fluoroimmunoassay under the assumption that no significant metabolism of morphine occurred during the study period, before recirculation of morphine had occurred. During this period, the only likely source for metabolism of morphine is the lungs. Metabolism of morphine does not occur in isolated, perfused rabbit lung [27] or in the lungs of patients [28].

Measurements were performed on an Abbott TDx Analyzer. Whole blood 0.3 ml was mixed with absolute alcohol 0.05 ml and saline 0.3 ml and vortexed. The solution was centrifuged (TDx centrifuge, 13000 r.p.m. for 10 min) and 75 µl of the supernatant added to the TDx cups. The TDx opioids reagent pack was used. The TDx Analyzer was calibrated with standard whole blood samples at concentrations of 0, 125, 500, 1000 and 2000 µg ml^{-1}. Spiked controls of 374 and 2888 ng ml^{-1} were analysed with each batch. The deviations of these known values were 0.5 and 4% of the true value and the between-run coefficients of variation were 7.1 and 6.8%, respectively.

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VASODILATOR PROPERTIES OF NITROGLYCERIN AND ISOSORBIDE DINITRATE DURING CARDIOPULMONARY BYPASS†

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SUMMARY

In a placebo-controlled trial, we have studied the vasodilator properties of bolus doses of nitroglycerin (TNG) and isosorbide dinitrate (ISDN) in 32 patients during cardiopulmonary bypass with a constant pump flow. Blood volume of the venous reservoir and mean arterial pressure were recorded for 10 min after drug administration to detect changes in venous capacitance and arteriolar resistance, respectively. The venous capacitance-increasing effects of TNG 200 µg and ISDN 1600 µg were initially identical and significant at 2 and 3 min after the bolus. Thereafter, the effect of TNG began to decline, while that of ISDN remained significant until the end of the study. TNG 200 µg decreased arterial pressure slightly more than ISDN 1600 µg, but the effect of both drugs lasted for only 1–2 min. TNG and ISDN were equipotent in increasing venous capacitance when administered in a bolus dose ratio of 1:8 during CPB, but the venodilator effect of ISDN lasted longer than that of TNG. The duration of the arteriolar dilator effect was very short with both drugs.

KEY WORDS

Anaesthetic techniques: hypotensive. Pharmacology: nitroglycerin, isosorbide dinitrate. Surgery: cardiopulmonary bypass.

Organic nitrates are commonly given i.v. for the treatment of myocardial ischaemia and pulmonary and systemic hypertension, in addition to providing controlled hypotension in surgical patients [1, 2]. In general, nitrates have a predominant effect on the venous side of the vasculature, with less effect on arteries. Thus nitrates decrease cardiac filling pressures relatively more than systemic vascular resistance, arterial blood pressure and cardiac output. However, there are *in vitro* [3, 4] and *in vivo* [5] studies showing that various organic nitrates have different potency and selectivity in their effects on the venous and arterial beds, although the results are in part conflicting. In some situations, for example in the presence of increased myocardial oxygen consumption in association with systemic hypotension as a consequence of ischaemia-induced left ventricular failure and dilatation of the heart, it may be beneficial to give a nitrate which is more selective in its effect on the venous than on the arterial vascular bed. In man it is possible to evaluate concomitantly the venous/venular and arterial/arteriolar vascular effects of drugs during the constant flow conditions of cardiopulmonary bypass (CPB) by observing changes in the volume of blood returning into the venous reservoir and by measuring systemic arterial pressure, respectively [6–11]. In this study, we have compared the vasodilator properties of two organic nitrates available for i.v. use (nitroglycerin (TNG) and isosorbide dinitrate (ISDN)). These two nitrates have been reported to have a differing selectivity in their *in vitro* vascular effects [3].

PATIENTS AND METHODS

Patients

Forty-one patients were admitted originally to the study. They were studied double-blind after informed consent and Ethics Committee approval. They were allocated randomly to four groups to receive placebo (0.9% sodium chloride), TNG 200 µg (Nitro, Orion Pharmaceutica, Espoo, Finland), ISDN (Nitrosid, Pharmacal, Helsinki, Finland) 800 µg or ISDN 1600 µg. Chronic medication (long-acting nitrates, calcium channel blockers and beta adrenergic receptor blockers) was continued until the morning of surgery. Only patients meeting the following criteria were included in the study: absence of vasoactive drugs before or during the study; absence of mechanical problems in venous return during CPB; mean arterial pressure (MAP) 50–80 mm Hg at the time of the test drug administration; MAP less than 100 mm Hg during the study. On the basis of these criteria, 32 patients were studied; nine of the original 41 patients were excluded from the trial—three patients because of technical problems in venous return, three because of hypertension during the study (MAP > 100 mm Hg) and three patients because of the need to give an additional dose of cardioplegic solution during the study.

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TABLE I. *Preoperative patient data (mean (range or SEM) or number of patients). TNG = Nitroglycerin; ISDN = isosorbide dinitrate*

	Group			
	Placebo	TNG 200 µg	ISDN 800 µg	ISDN 1600 µg
Sex (M/F)	8/0	5/3	6/2	6/2
Age (yr)	52 (40–63)	59 (50–71)	54 (43–65)	61 (48–72)
Weight (kg)	83 (3)	77 (5)	75 (4)	78 (4)
Height (cm)	176 (2)	168 (3)	169 (3)	169 (2)
Ejection fraction of left ventricle (%)	47 (5)	53 (7)	68 (5)	56 (7)
Medication				
Beta-adrenergic blocker	6	5	7	4
Calcium channel blocker	8	6	4	7
Nitrate	7	7	8	7

Anaesthesia

All patients were premedicated i.m. with hyoscine and morphine in doses of 6 and 200 µg kg^{-1}, respectively. Before induction of anaesthesia, intravascular catheters were inserted under local anaesthesia. Anaesthesia was induced with fentanyl 30 µg kg^{-1} and diazepam 0.1 mg kg^{-1}. Tracheal intubation was facilitated with pancuronium 0.1 mg kg^{-1}. Anaesthesia was maintained with an infusion of fentanyl 0.3 µg kg^{-1} min^{-1} until the start of CPB, when the dose was reduced to 0.15 µg kg^{-1} min^{-1}. During surgery before CPB, anaesthesia was supplemented with enflurane or halothane, and incremental doses of pancuronium were given when needed. After induction of anaesthesia, the lungs were ventilated mechanically with a mixture of oxygen and air ($F\text{I}_{O_2} = 0.5$) and normocapnia was maintained by monitoring end-tidal carbon dioxide concentration and by intermittent blood-gas analyses. During CPB the lungs were disconnected from the ventilator.

Cardiopulmonary bypass

The aorta and superior and inferior venae cavae were cannulated and the left ventricular decompression tube was introduced through a pulmonary vein. CPB was conducted with a semi-occlusive roller pump (Stöckert, Munich, FRG) and a bubble oxygenator (S100A, Shiley, Irvine, USA). The CPB circuit was primed with 2000 ml of Ringer's acetate–gluconate solution and heparin 5000 u. During CPB, heparin was given to maintain the activated clotting time greater than 480 s. A non-pulsatile pump flow of 2.4 litre min^{-1} m^{-2} was used during the cooling and rewarming phases. After achievement of moderate hypothermia (29 °C nasopharyngeal temperature), the pump flow was maintained at 1.8 litre min^{-1} m^{-2}. Oxygen 1 litre per litre of pump flow, was added into the oxygenator. Myocardial protection during aortic cross-clamping was achieved with systemic hypothermia, topical cooling of the heart and cold crystalloid cardioplegic solution (Plegisol, Abbot, North Chicago, U.S.A.). The cardioplegic solution was given at 20-min intervals.

Study design

The study was undertaken during stable hypothermia between administration of two doses of cardioplegic solution and maintaining the blood flow and the left ventricular decompression force constant. MAP and the blood level in the reservoir (venous return) were measured. Although the pump flow was non-pulsatile in nature, a small pulse pressure, 10 mm Hg on average, was generated. MAP was determined from the mid-point of the pulse pressure curve. During the 15-min study, radial artery pressure was recorded continuously (Nihon Kohden, Tokyo, Japan) and venous return was noted at 1-min intervals. Before administration of the test drug, arterial pressure and venous return were monitored for 5 min. After this control period, one of the test drugs was given as a bolus dose from a glass syringe into the venous side of the CPB circuit and haemodynamic effects were recorded for 10 min. The drugs were dissolved in 10 ml of 0.9% saline solution.

Statistical analyses

Two-way analysis of variance (ANOVA) for repeated measures was used to assess the significance of overall haemodynamic changes between the groups. This assessment was used separately for the data of the control period and those of the study period proper. After this, the effects of each drug were compared with placebo by two-way analysis of variance. At each 1 min of the study period, the differences between the groups in changes in MAP and reservoir blood volume were tested with one-way analysis of variance, followed by multiple comparisons with the unpaired t test and Bonferroni corrections. Patient data and study conditions were compared using one-way analysis of variance. Frequencies were compared with the χ^2 test. $P < 0.05$ was considered statistically significant. The results are presented as mean (SEM).

RESULTS

All four groups were similar in preoperative patient characteristics, haemodynamic changes during the control period and conditions at the beginning of the study (tables I, II).

Change in reservoir blood volume (fig. 1)

TNG 200 µg, ISDN 800 µg and ISDN 1600 µg decreased reservoir blood volume significantly more than placebo. When compared with placebo, TNG 200 µg decreased reservoir volume significantly at

TABLE II. *Study conditions before drug administration (mean (SEM)). TNG = Nitroglycerin; ISDN = isosorbide dinitrate*

	Group			
	Placebo	TNG 200 μg	ISDN 800 μg	ISDN 1600 μg
Pump flow (litre min^{-1} m^{-2})	1.78 (0.03)	1.79 (0.02)	1.74 (0.05)	1.76 (0.03)
Mean arterial pressure (mm Hg)	64 (4)	66 (3)	62 (3)	73 (2)
Rectal temperature (°C)	30.3 (0.5)	30.8 (0.4)	29.7 (0.5)	30.9 (0.3)
PCV (%)	27 (1)	26 (2)	24 (1)	25 (1)
Change during the 5-min control period				
Mean arterial pressure (mm Hg)	+7.5 (2.9)	+7.5 (2.1)	+7.5 (2.6)	+10.6 (2.2)
Reservoir volume (ml)	−189 (46)	−216 (77)	−223 (37)	−173 (59)

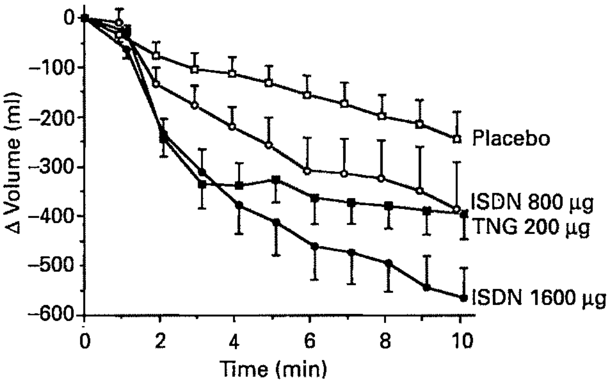

FIG. 1. Change in reservoir volume (venous return) after a bolus dose of placebo, nitroglycerin (TNG) and two doses of isosorbide dinitrate (ISDN).

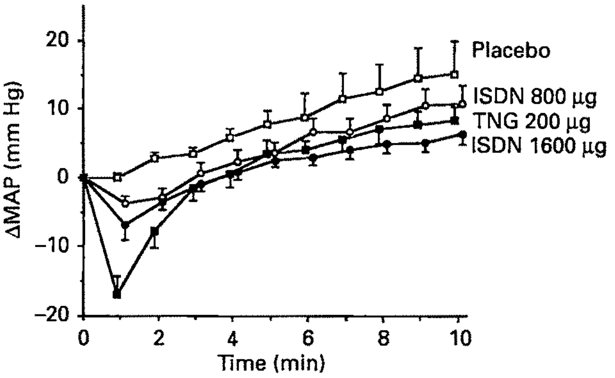

FIG. 2. Change in mean arterial pressure (MAP) after a bolus dose of placebo, nitroglycerin (TNG) and two doses of isosorbide dinitrate (ISDN).

2–4 min and ISDN 1600 μg at 2–10 min after drug administration. Although the overall decrease with time for ISDN 800 μg was significant compared with placebo according to two-way ANOVA, the exact timing of this decrease could not be determined by one-way ANOVA as analysed at each 1 min.

Change in mean arterial pressure (fig. 2)

TNG 200 μg decreased MAP more than the other drugs at 1 min after the drug bolus. At 2 min after injection, both TNG 200 μg and ISDN 1600 μg decreased MAP more than placebo. The effect of ISDN 800 μg on MAP was not significantly different from placebo.

DISCUSSION

The present study was performed to evaluate the vasodilator properties of bolus doses of TNG and ISDN during hypothermic CPB. We showed that TNG and ISDN, when administered in a dose ratio of 1:8, were equipotent in respect to the peak venodilator effect, but that the duration of effect was longer with ISDN. In this dose ratio, TNG caused more rapid arteriolar dilatation than ISDN.

Because the cardiac responses to changes in peripheral vascular tone are eliminated during CPB, this procedure allows the investigation of both arteriolar and venous effects of drugs in cardiac surgical patients. However, the use of CPB as a method of evaluating vascular effects of drugs requires steady state conditions. Therefore, we maintained pump flow constant during the measurements. Furthermore, no additional cardioplegic solution was given between the two administrations of the study period and the suction force exerted on the left ventricular decompression tube was maintained constant. Particular attention was paid to eliminating technical problems with venous return by avoiding any major manipulation and positioning of the heart during the study. In addition, the trial was performed after reaching steady state hypothermia and the infusion of fentanyl was continued unaltered throughout the study. In spite of these efforts to stabilize conditions, there was a continuous increase in arterial pressure and a decrease in reservoir blood volume during CPB [6, 9], and therefore we compared our data with a control group. With this study design, acute changes in arterial pressure and venous return reflect drug-induced changes in vascular tone of arterial and venous beds, respectively.

Venodilatation is maximal with small doses of nitrates, only little additional dilatation occurring when the dose is increased [12]. Systemic arteries begin to dilate also with small doses but, in contrast to veins, arteries continue to dilate with increasing doses. Arteriolar dilatation occurs only with large doses of nitrates [12]. The increase in venous capacitance indicates decreased preload and reduction in heart size and ventricular wall tension. Arterial and arteriolar dilatation lead to a decrease in systemic arterial pressure and systemic vascular resistance [2, 12]. The decreases in preload and afterload cause a reduction in myocardial oxygen demand

[2]. Furthermore, nitrates improve myocardial oxygen supply by dilating epicardial coronary arteries and by increasing subendocardial blood flow as a result of reduced ventricular wall tension [12]. All these changes improve myocardial oxygen balance and are beneficial for ischaemic heart.

The more sensitive response of veins and venules to nitrates compared with arteries and arterioles is evident in this study: the venous effect caused by nitrates lasted longer than that in the arterial bed and the venodilatory effect was significant with time also with the smaller dose of ISDN, while the pressure effect was not. The present study confirms our earlier observation that nitrates affect the venous side more than the arterial side of the vasculature during CPB, in spite of intra-arterial administration [6].

It is not clear if the venous responses to TNG 200 µg and ISDN 1600 µg were maximal. However, the acute venodilator response to ISDN 800 µg was less marked than that to ISDN 1600 µg or TNG 200 µg. Thus our results show that, on a weight basis, TNG is more than four times (possibly eight times) as potent as ISDN in its peak venodilator activity when given as a bolus during hypothermic CPB. Toyoda, Hisayama and Takayanagi [4] also found that the potency order of three nitrates in dilating isolated veins and arteries was TNG > ISDN > ISMN (isosorbide 5-mononitrate). The relative contributions of ISDN and its active metabolite, ISMN, to the vascular responses observed in the present study remain unclear. The greater potency of TNG as an arteriolar dilator compared with ISDN is supported by the findings of Durkin and associates [13], who compared the efficacy of TNG and ISDN infusions in the management of perioperative hypertension during coronary artery surgery. With a mean dose ratio of approximately 1:2, TNG was more successful than ISDN in decreasing arterial pressure.

There seem to be differences also in the selectivity of the effects of various nitrates on veins and arteries. Toyoda, Hisayama and Takayanagi [4] compared the relaxant effects of TNG, ISDN and ISMN on isolated femoral veins and arteries. All nitrates dilated both veins and arteries, but ISMN had the greatest venous selectivity. Stiefel and Kreye [3], studying the responses of isolated renal vessels of the rabbit, showed that ISDN and ISMN were 7–20 times more potent relaxants of veins than of arteries. The sensitivity of TNG was slightly greater in veins than arteries in small concentrations, but similar in veins and arteries in greater concentrations. Our results suggest that, in a dose ratio with about equipotent venodilator activity, TNG caused slightly more prominent decrease in arterial pressure than ISDN. This finding is consistent with those of Cintron and colleagues [14]. They administered TNG or ISDN to patients with acute myocardial infarction by an i.v. infusion in a mean dose ratio of approximately 1:4 and found that, after about 1 h of infusion with a similar decrease in pulmonary capillary wedge pressure and systolic arterial pressure, cardiac output had increased significantly more with TNG than with ISDN; this suggests that systemic vascular resistance may have decreased more with TNG than with ISDN. These results suggest that ISDN has a more selective action on venous vasculature than TNG. However, Rezakovic and colleagues [5], who compared TNG and ISDN in stoichiometrically equivalent doses by infusing them in a dose ratio 1:1.5 over 30 min in patients with acute myocardial infarction, found that TNG influenced predominantly pulmonary artery pressure and cardiac filling pressures, while ISDN affected cardiac output and systemic vascular resistance. They concluded that TNG is predominantly a venous dilator, while ISDN is a mixed vasodilator.

During the changing conditions of CPB, only short periods of relative stability are available for observation of drug effects. Therefore, we used bolus dose administration of drugs and our conclusions are applicable only to this mode of administration. Administering nitrates by an infusion would probably result in a different dose ratio, mainly because of the longer duration of action of ISDN/ISMN relative to TNG. Cintron and colleagues [14] found that, after producing a similar decrease in pulmonary capillary wedge pressure with TNG and ISDN in a dose ratio of 1:4 in patients with acute myocardial infarction, the maintenance of the decrease in the wedge pressure required progressive increase in TNG dosage, while the dose of ISDN remained essentially unchanged. Further, Davis and co-authors [15], giving continuous infusion of either TNG or ISDN during the prebypass period in patients undergoing coronary artery surgery, achieved a similar control of arterial pressure with a total dose ratio of approximately 1:1. Our results may have clinical significance, as a bolus dose of a nitrate may be a suitable way of rapidly increasing venous capacitance or decreasing systemic vascular resistance during the transient haemodynamic changes in patients undergoing CPB.

ACKNOWLEDGEMENT

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ACCURACY OF TEXT ENTRIES WITHIN A MANUALLY COMPILED ANAESTHETIC RECORD

L. ROWE, D. C. GALLETLY AND R. S. HENDERSON

SUMMARY

We have examined the accuracy of text entries within a manually compiled anaesthetic record by comparing the record of the anaesthetist with that of an observer, present throughout the procedure but whose sole purpose was the documentation of perioperative events. Eighty-six items of information were analysed for accuracy from 197 records. The mean proportion of omissions was 35% and the mean proportion of incorrect entries was 3.4%. Where no entry should have been made, the mean proportion of unwarranted entries was 1%. Accuracy varied according to the information contained; however, omissions were common for preoperative status, fluids, tourniquet use, aspects of monitoring, local anaesthesia and intraoperative problems. The most consistently accurate information was the description of the patient and that relating to intraoperative i.v. drug use. Inaccuracy was common for the majority of sites on the record, irrespective of their reflecting on the anaesthetist's performance. We suggest, therefore, that the reason for this inaccuracy of data was not related principally to anaesthetists' defensiveness, but may reflect their attitudes to the record's value and response to inadequacies in its design. The observed deficiencies in recording accuracy may affect patient safety during future anaesthesia and has relevance to medico-legal and epidemiological research.

KEY WORDS

Records, anaesthesia. Accuracy.

The manually compiled anaesthetic record is recognized widely as being an important component of anaesthetic care [1]. Studies have shown, however, that when recording physiological variables, anaesthetists tend to understate extreme values and smooth out normal physiological fluctuations [2–6]. Although some authors consider this to be "clinically relevant filtering of physiological artefact" [5] and of no real significance, others suggest it represents an anaesthetist's unconscious defence strategy, fewer extreme recordings implying better case management [4]. In a recent survey of New Zealand anaesthetists, data manipulation (either intentional omission or the recording of incorrect information) was found to be a common and conscious act [1].

Previous studies of the accuracy of the anaesthetic record have focused on the accuracy of physiological recordings. However, these make up only a part of the total record content and their correct interpretation requires a knowledge of the additional text entries which specify the drugs, their time of administration and dose, fluids administered, ventilatory information and problems encountered. To our knowledge, no comprehensive study has examined the accuracy of these accompanying data. In this study, we examined the accuracy of these text entries by comparing the actual record produced by anaesthetists with that of an anaesthetist observer who took no part in the anaesthetic management and whose sole function was the compilation of an accurate and comprehensive account of the perioperative course.

METHODS

The study was conducted over a 4-month period at a large New Zealand public hospital. After prior approval from the Ethics Committee, anaesthetists at that hospital were informed that an observer would be present throughout some of their cases and that the purpose of this was to audit the methods of anaesthesia used within the department. They were not told the exact nature of the study and none knew until immediately before induction of anaesthesia, that a specific case was being observed.

Two hundred patients undergoing general or major regional anaesthesia were studied. They were selected at random on the morning of surgery from operating theatre schedules and included patients undergoing gynaecological, orthopaedic, ENT, ophthalmological or general surgery. Owing to time constraints, cardiothoracic and neurosurgical cases were excluded, as were cases expected to last longer than 3 h.

From the time of arrival in the operating theatre area until discharge from the recovery room, all patients were accompanied by an observer, a post-Fellowship registrar with 5 years experience in

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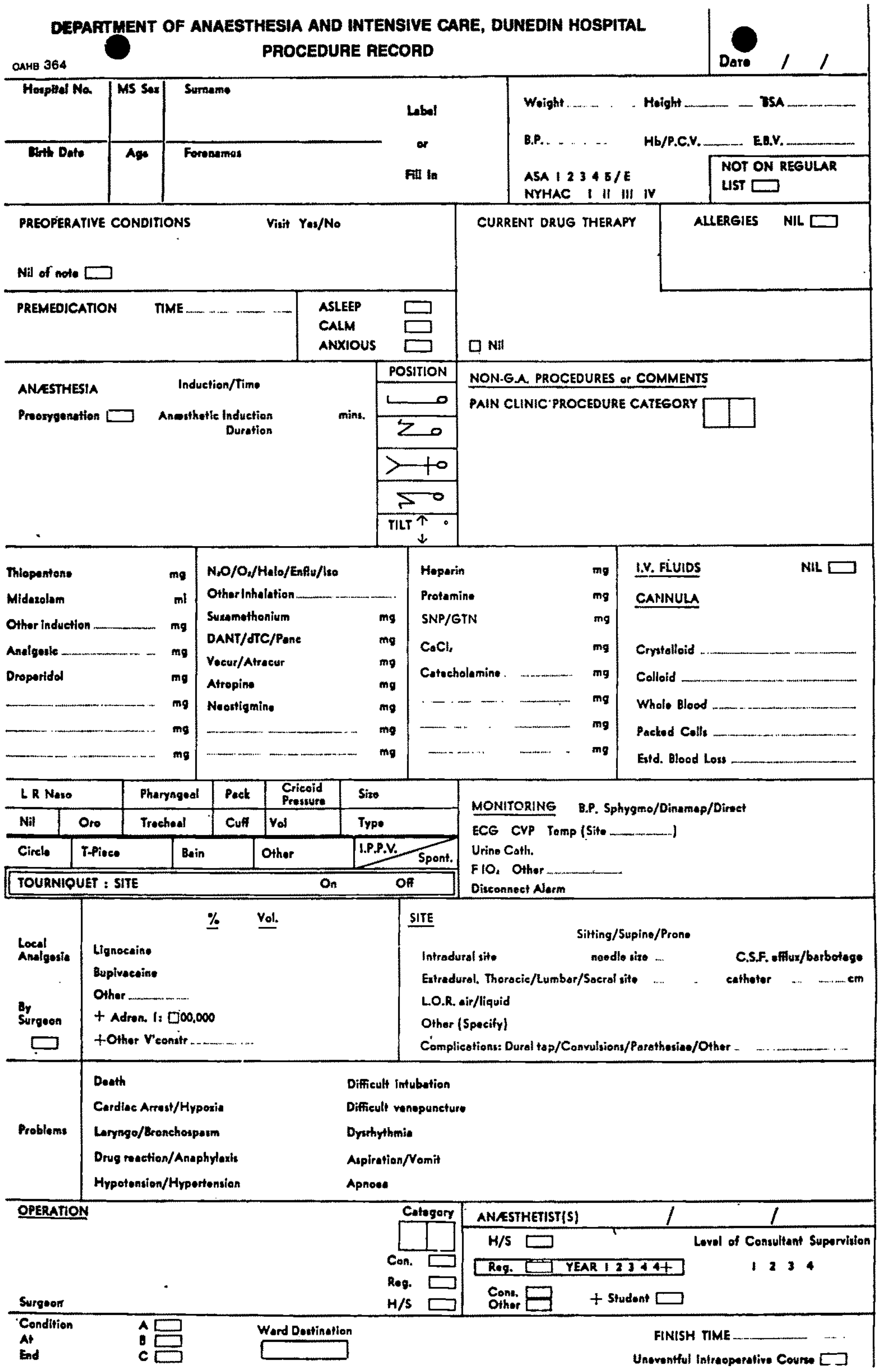

DEPARTMENT OF ANAESTHESIA AND INTENSIVE CARE, DUNEDIN HOSPITAL
PROCEDURE RECORD
OAHB 364
Date / /

Hospital No. | MS Sex | Surname | Label or Fill In
Birth Date | Age | Forenames

Weight ____ Height ____ BSA ____
B.P. ____ Hb/P.C.V. ____ E.B.V. ____
ASA 1 2 3 4 5 / E
NYHAC I II III IV
NOT ON REGULAR LIST ☐

PREOPERATIVE CONDITIONS Visit Yes/No
Nil of note ☐

CURRENT DRUG THERAPY
☐ Nil

ALLERGIES NIL ☐

PREMEDICATION TIME ____
ASLEEP ☐
CALM ☐
ANXIOUS ☐

ANÆSTHESIA Induction/Time
Preoxygenation ☐ Anæsthetic Induction Duration mins.

POSITION
TILT ↑ ↓ °

NON-G.A. PROCEDURES or COMMENTS
PAIN CLINIC PROCEDURE CATEGORY ☐☐

Thiopentone	mg	N₂O/O₂/Halo/Enflu/Iso		Heparin	mg	I.V. FLUIDS	NIL ☐
Midazolam	ml	Other Inhalation ____		Protamine	mg	CANNULA	
Other induction ____	mg	Suxamethonium	mg	SNP/GTN	mg		
Analgesic ____	mg	DANT/dTC/Panc	mg	CaCl₂	mg	Crystalloid ____	
Droperidol	mg	Vecur/Atracur	mg	Catecholamine ____	mg	Colloid ____	
____	mg	Atropine	mg	____	mg	Whole Blood ____	
____	mg	Neostigmine	mg	____	mg	Packed Cells ____	
____	mg	____	mg	____	mg	Estd. Blood Loss ____	
		____	mg				

L R Naso		Pharyngeal	Pack	Cricoid Pressure	Size
Nil	Oro	Tracheal	Cuff	Vol	Type
Circle	T-Piece	Bain	Other		I.P.P.V. / Spont.

TOURNIQUET : SITE On Off

MONITORING B.P. Sphygmo/Dinamap/Direct
ECG CVP Temp (Site ____)
Urine Cath.
F IO₂ Other ____
Disconnect Alarm

Local Analgesia
By Surgeon ☐
% Vol.
Lignocaine
Bupivacaine
Other ____
+ Adren. 1: ☐00,000
+ Other V'constr ____

SITE
Sitting/Supine/Prone
Intradural site needle size ____ C.S.F. efflux/barbotage
Extradural. Thoracic/Lumbar/Sacral site ____ catheter ____ cm
L.O.R. air/liquid
Other (Specify)
Complications: Dural tap/Convulsions/Parathesiae/Other ____

Problems
Death
Cardiac Arrest/Hypoxia
Laryngo/Bronchospasm
Drug reaction/Anaphylaxis
Hypotension/Hypertension
Difficult intubation
Difficult venepuncture
Dysrhythmia
Aspiration/Vomit
Apnoea

OPERATION
Category ☐☐
Con. ☐
Reg. ☐
H/S ☐
Surgeon

ANÆSTHETIST(S) / /
H/S ☐
Reg. ☐ YEAR 1 2 3 4 4+
Cons. ☐
Other ☐
+ Student ☐
Level of Consultant Supervision
1 2 3 4

Condition At End
A ☐
B ☐
C ☐
Ward Destination ☐
FINISH TIME ____
Uneventful Intraoperative Course ☐

FIG. 1. The anaesthetic record form.

anaesthesia. The observer took no part in the clinical management and communicated with theatre staff only when this was essential (in one case the observer took over for a short period when the anaesthetist left to attend an emergency).

The observer entered intraoperative data onto a comprehensive five-page record. This included information which would be entered normally onto the case note anaesthetic record, and additional information detailing the anaesthetic course and system errors (the subject of a separate paper). Data included all aspects of drug, gas and fluid administration, i.v. cannulation, monitoring, breathing system and ventilation variables, positioning, tourniquet use and local anaesthesia administration. All abnormal physiological events noted by the observer were recorded, as were all problems and system errors. Where non-invasive arterial pressure monitors were used (Dinamap), all digital recordings were noted. The patient's preoperative condition was assessed and recorded by independent clinical examination, reference to case notes and laboratory investigations.

Two days after anaesthesia, each patient's case records were retrieved and a copy of the actual anaesthetic record was made. This record comprises four sides (two sheets) for data collection, two covering the intraoperative period. The first of these (fig. 1) includes the text entries and is intended as a comprehensive summary of the anaesthetic course. A carbon copy of this sheet is kept for computer entry and later departmental review of such matters as changing patterns of drug utilization, trainee supervision and intraoperative complications. This summary sheet was the subject of the present study. The second intraoperative data sheet comprises a graphical record of physiological measurements. While some anaesthetists include drug and fluid information on this graphical record, it is expected by the department that an accurate summary appears on the text entry sheet.

The anaesthetic record examined in this paper is, in our opinion, representative of traditional manually compiled records in widespread use, although it may specify in more detail than others, the entries required. As is currently a common trend, this itemized format had been chosen because entries were intended for computer input.

The data from the observer's and the actual patient record (summary sheet) were categorized and entered onto computer spreadsheets (Statview SE) for statistical comparison.

RESULTS

In three cases an anaesthetic record could not be found within the patient's case notes. Examination of record accuracy was therefore limited to the remaining 197 records.

Eighty-six specific items of information from the anaesthetic record (fig. 1) were examined for accuracy and for each item we calculated the number of records in which:

(1) entry of that item was expected (E);

(2) the expected entry had been omitted (O);

(3) the expected entry was made but was incorrect (I);

(4) no information should have been entered but an inappropriate entry was made (N).

From these were calculated the proportion of omissions (O/E), the proportion of incorrect entries (I/E) and the proportion of inappropriate entries where no entry was expected (N/(197-E)) (table I).

For the 86 entry sites examined, the total number of expected entries was 8231—a mean of 41.8 per record. Where an entry was expected, the mean proportion of omissions was 35% and the mean proportion of incorrect entries was 3.4%. Where no entry should have been made, the mean proportion of unwarranted entries was 1%.

Recording accuracy was greatest for demographic information (patient name and hospital number being attached to the record using preprinted labels). Sites for anthropomorphic and preoperative clinical and laboratory data showed high proportions of omission. In particular, those for blood volume, NYHAC (New York Heart Association Classification), preoperative haemoglobin concentration, and patient height were almost invariably omitted. It is probable that these relate to a lack of perceived usefulness of the data to the anaesthetist and may be more relevant to other types of surgery not included in this study (e.g. cardiac).

Potentially more useful data such as ASA, preoperative arterial pressure and patient weight were also omitted commonly. For ASA, there was some discrepancy between the observer's and anaesthetist's assessment. However, consistent with previous published studies [7], there was no apparent trend or bias towards one extreme of values and, where there was a discrepancy, the observer's and anaesthetist's grading varied at most by one ASA grade in either direction.

A number of preoperative conditions and medications were not recorded, although they could have been influential in determining the choice of drugs or anaesthetic technique. Because these entry sites are open-ended, it might be expected that omissions would be frequent. In many cases, however, the "nil" boxes were ticked also; although possibly ticked in error, this suggests that anaesthetists were unaware of these conditions and drugs. The drugs omitted most commonly were oral contraceptives (15 records), antibiotics (six), bronchodilators (seven) and regular aspirin (five). The most commonly omitted preoperative conditions were smoking (36 records), hypertension (17), recent upper respiratory tract infection (18), other pulmonary/bronchospastic disease (21), haematological abnormalities (12), psychiatric disturbances/dementia (10) and obesity (eight). In two records, a previous documented history of difficult intubation was not noted. Of 29 records of patients with a history consistent with genuine drug allergy, the fact was not noted in 16, and in four of these cases the "nil allergy" box was ticked.

Premedication data were omitted in approximately 15–20% of records, although the drug was documented more commonly than dose, which in turn was more accurate than premedication time.

Intraoperative drugs tended to be documented more accurately than premedicants. The most accurate were non-depolarizing neuromuscular blocking drugs, suxamethonium and the opioids. The dose used was less accurate than the drug itself; this was especially so for the induction agent, where the drug was not named in 5% of records and the dose was either incorrect or omitted in 22%. The volatile agent/gas used was poorly documented (13% omitted or incorrect) and, in 11 cases, patients received halothane for maintenance without this being recorded (representing 9% of all patients receiving halothane).

Fluid and i.v. therapy data were documented poorly: 27% of fluids were not recorded and the volume was inaccurate or omitted in 73% of records.

Accuracy of airway information varied, the type of tracheal tube being recorded for almost 95% of patients, while tube size was commonly incorrect and cuff volume was rarely recorded. Although an

TABLE I. *Data entry site: number of records where an entry was expected (E), proportion (%) of omissions (O/E) and incorrect entries (I/E) at those sites where an entry was applicable, and proportion (%) of inappropriate entries at those sites where no entry should have been made (N/197-E).— = Not applicable*

Data entry site	E	Omitted (%)	Incorrect (%)	Inappropriately entered (%)
Date	197	1	4	—
Name	197	0	0	—
Hospital number	197	0	0	—
Operation	197	3	4	—
Weight	197	49	2	—
Height	197	96	0	—
Blood volume	197	100	0	—
Preop. AP	197	82	3	—
Preop. Hb concn	197	97	0	—
ASA	197	22	21	—
New York Heart Ass. Class.	197	99	1	—
Preop. visit	197	20	4	—
Preop. condition	157	72	1	0
Nil of note box	40	43	0	16
Current therapy	98	59	1	0
Nil curr. therapy box	99	51	0	13
Allergies	29	55	0	2
Nil allergies box	168	47	0	14
Asleep/calm/anxious	197	19	17	—
Premedicant drug	147	14	2	0
Premedicant dose	147	19	6	0
Premedicant time	147	22	8	0
Induction time	197	4	4	—
Induction duration	197	28	10	—
Preoxygenation	31	29	0	6
Anaesthesia	197	15	0	—
Position	197	14	1	—
Induction drug	174	5	0	4
Induction drug dose	174	11	11	0
Analgesic drug	139	4	0	0
Analgesic dose	139	6	6	0
Gas and vapour	174	6	7	0
Suxamethonium dose	32	3	0	0
Competitive NMB	79	1	0	0
Competitive NMB dose	79	1	3	0
Atropine/neostigmine dose	77	10	0	0
Other drugs	38	8	0	0
I.v. fluid type	30	27	0	1
I.v. fluid volume	30	43	30	0
Nil fluid box	167	64	0	7
Cannula size	195	22	4	0
Cannula site	195	36	7	0
Tracheal tube type	104	6	0	0
Tracheal tube size	104	8	11	0
Tracheal tube cuff vol.	83	75	2	0
Trach. tube cuff used	83	8	0	2
Oropharyngeal airway	61	10	0	21
Spontaneous ventilation	104	20	0	2
IPPV	84	17	0	9
Circle	154	14	0	2
T-piece	20	20	0	1
Other circuit	19	11	0	1
Tourniquet site	27	52	0	0
Tourniquet time	27	63	7	0
AP monitor	185	6	0	17
Dinamap (NIAP)	168	10	0	3
Direct AP	3	0	0	0
ECG monitored	189	6	0	50
CVP monitored	0	—	—	0
Temperature monitored	7	29	0	0
Urine catheter	5	100	0	0
$F\mathrm{I}_{\mathrm{O}_2}$ monitored	168	27	0	17
Oximeter used	109	26	0	0
Nerve stimulator used	30	37	0	1
LA by surgeon box	15	60	—	1
LA block type	50	14	4	0
Lignocaine used	23	39	0	2
Lignocaine %	23	39	26	1
Bupivacaine used	30	0	0	1
Bupivacaine %	30	3	13	1

(continued)

TABLE I (*cont.*)

Data entry site	E	Omitted (%)	Incorrect (%)	Inappropriately entered (%)
Adrenaline concentration	17	29	24	1
Other vasoconstrictor	8	75	0	1
Position (spinal/extrad.)	13	38	31	1
Spinal needle	8	12	0	0
LA complication	11	82	0	0
Death	0	—	—	0
Cardiac arrest	0	—	—	0
Hypoxia	13	100	0	0
Laryn./bronchospasm	16	69	0	0
Hypotension/hypertension	8	100	0	0
Difficult intubation	9	56	0	0
Difficult venepuncture	14	100	0	0
Arrhythmia	33	67	0	0
Aspiration	0	—	—	0
Vomiting	3	100	0	0
Apnoea	0	—	—	0

oropharyngeal airway was inserted in only 61 patients, its use was documented in 89. For approximately 15% of patients, a record of the breathing system was omitted.

Despite its importance, both the site and timing of tourniquet use was omitted in more than 50% of relevant cases.

Monitoring equipment was documented most accurately for arterial pressure and ECG ($\leqslant$ 10% omission), although for other monitors (temperature, urine catheter, $F\text{I}_{\text{O}_2}$, pulse oximeter, nerve stimulator) the rate of omission was 25% or greater.

Fifty patients received local anaesthetic agents either alone or as part of a combined technique with general anaesthesia. In approximately 40% of patients in whom lignocaine was used, the fact was not documented and in 65% the concentration used was not recorded or was inaccurate. Similarly, the use of a vasoconstrictor was documented poorly, for adrenaline the concentration being omitted or incorrect in 53%.

In 11 patients a problem occurred with the local anaesthesia (generally poor block) but was not noted in nine of these.

The area of the anaesthetic record set aside for documentation of problems had a low accuracy, invariably because of data omission. Difficulties with venepuncture (three or more attempts) were not recorded and difficulties with intubation (two or more attempts) were recorded in only 45% of cases. None of the episodes of hypoxaemia (observed central cyanosis), vomiting, hypertension (> 180 mm Hg) or hypotension (< 70 mm Hg) was recorded.

DISCUSSION

This present study has shown that the inaccuracy of anaesthetic record text entries is at least as significant as the inaccuracies in the recording of physiological variables. The most accurate records (other than basic demographic information) were those giving details of intraoperative drugs. Few other records gave less than a 10% rate of omission or inaccuracy.

The largest number of recording errors related to data omission, rather than the recording of false information. Our data indicate that a reviewer, when examining a completed record, should be most accepting of entries made and less certain with regard to the accuracy of absent information.

Analysis of physiological variables recorded manually onto anaesthetic records has demonstrated an apparent bias towards fewer extreme values and a smoother physiological course than occurs in reality. Common explanations given for this bias include poor memory or the need for retrospective recording at times of anaesthetic activity (such as during induction) and the filtering of irrelevant artefact or physiological fluctuation [5]. It is a widespread assumption, however, that failure to record physiological variables frequently represents the anaesthetist's defensive attitude towards outside scrutiny [4]. In this present study, we have observed a high degree of inaccuracy in anaesthetic record text entries, the majority of which do not contain medico–legally sensitive information and which do not reflect well or badly upon the anaesthetist's performance. This is consistent with a previous study [1] in which we found data manipulation of physiological variables to be uncorrelated with medico–legal concerns or willingness to use automatic recording devices, but variably correlated with other factors representing the anaesthetist's attitude towards the record form's purpose, relevance or adequacy of design.

One could argue that an anaesthetist's defensiveness is reflected in the low rate of documentation of morbidity and procedural difficulties. For these entries, however, the inadequate recording may simply reflect the lack of formal definition for each problem. Thus, of those problems and complications specifically listed, only death could be considered as sufficiently well defined to require no judgement (or allow no bias) on the part of the anaesthetist. Other problems, such as "difficult intubation" or "difficult i.v. cannulation", lack clear criteria for entry. Lunn [8] has noted the "folly of a design which permits mixture of fact with opinion, particularly when subsequent interpretation is anticipated". A standardized, clearly defined criterion (for example, in the case of difficult intubation, based on degree of visualization of the vocal cords) is probably a necessary requirement for subsequent analysis.

With the obvious exception of drug names, there are comparatively few differences between records in current use and those used half a century ago [9, 10], with our modern practice based largely upon "the traditional and not necessarily logical, nature of our habits" [11]. In recent years, however, the number of recordable physiological variables has increased greatly. Since anaesthetists spend between 10 and 15% [12–15] of intraoperative time completing the anaesthetic record, it is possible that the added demands from increased monitoring could further frustrate the task of accurate record completion. Given the degree of omission found in these records, it might also be argued that this time might be better devoted to direct patient care and that any attempt to reduce data omission while retaining a manual recording system would be likely to reduce further the time spent in patient monitoring. Conversely, it may be the case that the mental activity required for manual record keeping prompts patient observation.

A number of authors have suggested that the use of automated anaesthesia recording devices would improve the accuracy of anaesthesia documentation or increase the time spent in direct patient care [13, 16, 17]. Others have pointed out the problems with these devices [18] or have attempted to assess how these problems could be overcome [19]. However, in addition to accurate, automatically recorded physiological variables, correct interpretation requires accurate text entries. We have demonstrated in this study that these text entries are omitted frequently or are inaccurate, although it is possible that improvements in this aspect would occur with computer-based entry [20] and that further improvements in accuracy could be achieved using intelligent software systems which could reject inconsistencies and demand a correction at the time of data entry. While computer-based text entry systems using keyboard, barcode, light pen, touch screen or voice recognition have been devised and evaluated [17, 20–23], it is this aspect of automated recording which has proved the most difficult to implement and is one reason why completely automated methods have been slow to develop [11].

Many reasons have been cited for the production of anaesthetic records, including intraoperative review and trend detection, future patient management, medico–legal documentation, research and quality assurance. The requirements for each are different; however, inaccuracy has implications for all.

Future patient management. Data omission, the commonest form of text entry inaccuracy could have serious implications for future patient safety, as for example in those in whom exposure to halothane went undocumented. Where patient management is being planned, the absence of such information should not be accepted as reliable.

Quality assurance and research. Computer-based record reviews are undertaken commonly as part of quality assurance procedures and epidemiological research. It is apparent, however, that only a few text entry sites can provide accurate data on which to test research hypotheses or base a quality assurance analysis. Review of basic demographic features, drug usage and type of anaesthetic would, on the basis of our findings, give data of reasonable accuracy and be useful for monitoring operating theatre utilization [24, 25] and pharmaceutical usage. Quality assurance review of problems and complications, however, would collect only a small proportion of those cases in which problems occurred. When problems are recorded, these entries are reasonably accurate and, depending upon the analysis being performed, such data could be useful. However, comparison of records documenting a condition with those omitting such documentation (in order, for example, to ascertain factors associated with the production of minor morbidity) would be unlikely to provide data from which reliable conclusions could be drawn. Certainly, no reliable comparison could be made between different anaesthetists' performances, as an individual's entry criteria differ, as does the diligence of recording.

Medico–legal documentation. The anaesthetic record has an important role in medico–legal matters, although it is difficult to imagine how the current record could provide the basis for an accurate legal opinion. In this present study, the timing and doses of drugs were frequently incorrect, as were the fluid volumes, tourniquet times and site, and the problems encountered. It is therefore understandable why a frequent medico–legal problem for anaesthetists is the inaccuracy of their anaesthetic record. Powers and Gore noted with regard to intraoperative problems that their "improper and inadequate... notation... will require explanation and might even make certain cases legally indefensible" [26]. Dillon noted in regard to malpractice claims that records "almost always are grossly incomplete" [27].

In summary, this study has shown major inaccuracies in the text entries of manually compiled anaesthetic records. In conjunction with many studies which have demonstrated inaccuracy in the entry of physiological variables, we conclude that the manual record may present future anaesthetists with misleading information which could detrimentally affect patient safety. Although an anaesthetist may be reasonably (although not completely) confident that an event occurred if it is documented, he/she should not entertain such confidence if an event is not documented.

A previous record does not provide the anaesthetist with a reliable summary of preoperative condition, drug allergy or medications. Most importantly, the absence of recordings related to difficulty of intubation and exposure to halothane need to be viewed with considerable caution.

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TRANSCRANIAL DOPPLER SONOGRAPHY: EFFECTS OF HALOTHANE, ENFLURANE AND ISOFLURANE ON BLOOD FLOW VELOCITY IN THE MIDDLE CEREBRAL ARTERY

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SUMMARY

Systolic, diastolic, and mean blood flow velocity in the middle cerebral artery (Vs,mca; Vd,mca; Vm,mca) and pulsatility (Vs−Vd)/Vm of the waveform obtained were recorded in 51 patients before, during and after general anaesthesia. Transcranial Doppler (TCD) sonographic variables were measured in the awake patient and after induction of anaesthesia with thiopentone 5–6 mg kg^{-1}. After tracheal intubation, 17 patients received 0.8% halothane and 66% nitrous oxide in oxygen for 30 min (15 min normoventilation; 15 min hyperventilation). The inspired halothane concentration was then increased to 1.6% for 45 min (15 min normoventilation; 15 min hyperventilation; 15 min normoventilation with nitrous oxide replaced by oxygen). Enflurane (1.7% for 30 min and 3.4% for 45 min) was given to another 17 patients; 17 other patients received isoflurane (1.2% and 2.4%). Mean arterial pressure (MAP), nasopharyngeal temperature, end-tidal carbon dioxide concentration, inspired and end-tidal anaesthetic agent concentrations, haemoglobin concentration, PVC and TCD variables were measured at the end of each 15 min period. After recovery from anaesthesia, TCD variables were measured again. There were no intergroup differences in changes in MAP, nasopharyngeal temperature, haemoglobin concentration and PCV. Halothane, enflurane and isoflurane at low doses and normoventilation had little influence on TCD variables compared with awake values. In large concentrations with nitrous oxide in oxygen and normoventilation, there were differences between the volatile agents. Halothane increased blood flow velocities, but enflurane and isoflurane caused little change. Hyperventilation always decreased blood flow velocities and increased pulsatility. Six of 17 patients undergoing hyperventilation with 2.4% isoflurane and nitrous oxide in oxygen showed zero diastolic flow. This phenomenon was not observed in any patient receiving halothane or enflurane. With high doses of the volatile agents and normoventilation, blood flow velocities decreased in all groups after discontinuation of nitrous oxide. Our TCD results are compatible with the known effects of halothane, enflurane and isoflurane on cerebral blood flow (CBF). However, the relative changes in blood flow velocity and CBF may not be proportional with large doses of volatile agents, as a constant diameter of basal cerebral arteries may not be assumed under these conditions.

KEY WORDS

Anaesthetics, volatile: halothane, enflurane, isoflurane. Monitoring: transcranial Doppler.

Transcranial Doppler sonography (TCD) was introduced by Aaslid, Markwalder and Nornes in 1982 [1] and has become an important diagnostic method in neurology and neurosurgery. As TCD allows non-invasive and continuous measurement of blood flow velocities in basal cerebral arteries, the method may be suitable for intraoperative monitoring of cerebral haemodynamics. Assuming constant diameter of basal cerebral arteries, blood flow velocity should vary proportionally with cerebral blood flow (CBF) [2]. In symptomatic patients suffering from carotid artery disease, Bishop and colleagues [3] found significant correlations between the relative changes in cerebral blood flow velocity and CBF after changes in $P\text{CO}_2$.

Several investigators have used TCD during operations to monitor cerebral haemodynamics in carotid artery surgery [4–6] or open heart surgery with extracorporeal circulation [7, 8]. General anaesthesia is often maintained using halogenated anaesthetic agents such as halothane, enflurane and isoflurane, each of which may cause considerable alterations in CBF [9].

There is little information on the effects of halothane [10], isoflurane [11], or i.v. anaesthetics [12, 13] on TCD variables. In the present study, we have compared the effects of halothane, enflurane and isoflurane with and without nitrous oxide under varying ventilatory conditions to determine the impact of the anaesthetic regimen on intraoperative TCD monitoring.

PATIENTS AND METHODS

We studied 51 patients (table I) without signs or symptoms of cerebrovascular disease, undergoing general anaesthesia for trauma surgery. The study

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TABLE I. *Patient data (mean (range or* SD*)). No significant differences between groups*

	Halothane ($n = 17$)	Enflurane ($n = 17$)	Isoflurane ($n = 17$)
Age (yr)	31.5 (19–49)	31.4 (19–50)	25.8 (18–37)
Height (cm)	178 (9)	180 (8)	178 (7)
Weight (kg)	78.6 (10.4)	78.2 (10.9)	77.2 (11.2)

was approved by the Local Ethics Committee and written, informed consent was obtained from all patients.

After i.m. premedication (atropine, 0.1 mg kg^{-1}, promethazine 0.5 mg kg^{-1} and pethidine 1 mg kg^{-1}), transcranial Doppler sonography (TCD) was performed by a pulsed 2-MHz device (TC2-64, EME, Überlingen, FRG) using a handheld Doppler probe placed just above the zygomatic arch. At a depth of 45–55 mm, TCD signals of the middle cerebral artery (MCA) were identified after short compression of the ipsilateral common carotid artery. The site of insonation was marked. The contralateral MCA was investigated also, in the awake patient.

After a fixable flat probe was placed at the side of "best" insonation, control measurements were made. All TCD measurements included systolic (*V*s,mca), diastolic (*V*d,mca), and mean (*V*m,mca) blood flow velocity in the middle cerebral artery, and pulsatility (*V*s – *V*d)/*V*m. Further information on TCD methods may be obtained elsewhere [2, 14].

After induction of anaesthesia with thiopentone 5–6 mg kg^{-1} followed by vecuronium 2 mg, TCD variables were recorded again before tracheal intubation which was facilitated with suxamethonium 1 mg kg^{-1} (max. 100 mg). Further neuromuscular block was achieved with additional doses of vecuronium as required for the operative procedure. A nasopharyngeal temperature probe was placed in all patients after induction of anaesthesia.

After tracheal intubation, ventilation with 66% nitrous oxide in oxygen in a semi-closed circuit (Sulla 800V, Draeger) was regulated by continuous measurement of end-tidal carbon dioxide concentration (E'_{CO_2}) and halothane, enflurane or isoflurane was given in random order. An infra-red analyser (Normac, Datex) was used to measure inspiratory and end-tidal concentrations of the anaesthetic agents and E'_{CO_2}. The patients in the halothane group ($n = 17$) underwent ventilation with 0.8% halothane and tidal volume, ventilatory frequency, or both, were adjusted to maintain $E'_{CO_2} = 5.0\%$ (normoventilation) for 15 min, $E'_{CO_2} = 3.5\%$ (hyperventilation) for another 15 min. The inspired concentration of halothane was then increased to 1.6% for 45 min (15 min normoventilation, 15 min hyperventilation; 15 min normoventilation with nitrous oxide replaced by oxygen). The same procedure was used in 17 patients receiving enflurane (inspired concentrations 1.7% and 3.4%), and in 17 patients to whom isoflurane was given (1.2% and 2.4%). TCD variables were measured at the end of each 15-min period and after recovery from anaesthesia. Heart rate (ECG monitor), non-invasive arterial pressure (Dinamap, Critikon), PCV, haemoglobin concentration and $P\text{CO}_2$ (venous blood samples) were measured simultaneously.

Statistical methods consisted of one- and multidimensional analyses of variance. $P < 0.05$ was considered statistically significant.

RESULTS

Patients in the three anaesthetic groups ($n = 17$ each) did not differ significantly in age, weight or height (table I). Results for the halothane, enflurane and isoflurane groups are presented separately in tables II, III and IV, respectively, while changes in *V*m,mca and pulsatility may be compared between groups in figures 1 and 2, respectively.

In the awake patients, TCD variables were similar in all groups. After induction of anaesthesia with

TABLE II. *Data in the halothane group (mean* (SD)*). Vapour concentrations and type of ventilation are given in the first column.* V*s, mca,* V*d, mca,* V*m, mca = systolic, diastolic and mean blood flow velocity, respectively in the middle cerebral artery (mca); PI = pulsatility given as (*V*s,mca –* V*d,mca)/*V*m,mca;* FI_{hal}, FE_{hal} *= inspiratory and end-tidal concentrations of halothane; MAP = mean arterial pressure;* E'_{CO_2} *= end-tidal carbon dioxide partial pressure;* Pv_{CO_2} *= venous partial pressure of carbon dioxide;* T*ns = nasopharyngeal temperature; Hb = haemoglobin concentration.* $P < 0.05$ vs*:* * *awake values;* † *preceding data; significance marked for TCD parameters only. For further information see text*

	*V*s,mca (cm s^{-1})	*V*d,mca (cm s^{-1})	*V*m,mca (cm s^{-1})	PI	FI_{hal} (%)	FE_{hal} (%)	MAP (mm Hg)	E'_{CO_2} (%)	Pv_{CO_2} (kPa)	*T*ns (°C)	Hb (g%)	PCV (%)
Awake	86.8	44.7	60.1	0.705			98.5					
	(18.6)	(10.3)	(12.5)	(0.108)			(13.6)					
After	70.0	30.1	43.5*	0.950*			98.9					
induction	(15.4)	(10.6)	(12.2)	(0.212)			(13.5)					
0.8 vol%,	82.0	45.2	58.8	0.634†	0.71	0.44	92.1	5.04	5.3	35.8	13.3	40.2
normovent.	(14.8)	(10.3)	(11.3)	(0.133)	(0.14)	(0.18)	(10.4)	(0.09)	(0.4)	(0.6)	(1.1)	(3.4)
0.8 vol%,	62.0*	33.4	44.3	0.649	0.72	0.50	99.0	3.50	4.2	35.6	13.4	40.2
hypervent.	(10.4)	(6.6)	(7.5)	(0.109)	(0.15)	(0.18)	(14.5)	(0.12)	(0.4)	(0.6)	(1.0)	(2.9)
1.6 vol%,	102.8†	64.0*†	79.2*†	0.508*	1.48	0.87	101.4	5.04	5.3	35.6	13.4	40.2
normovent.	(25.5)	(20.4)	(21.7)	(0.129)	(0.17)	(0.18)	(15.8)	(0.08)	(0.3)	(0.6)	(1.3)	(3.7)
1.6 vol%,	82.5	47.8	60.2†	0.598	1.37	1.00	94.0	3.51	4.2	35.6	13.4	39.5
hypervent.	(20.2)	(13.9)	(16.1)	(0.114)	(0.15)	(0.17)	(14.3)	(0.06)	(0.4)	(0.6)	(1.2)	(3.4)
1.6 vol%,	83.1	48.1	61.6	0.574	1.66	0.98	96.4	4.98	5.3	35.7	14.0	41.6
normovent., no N_2O	(17.8)	(11.3)	(13.1)	(0.087)	(0.14)	(0.15)	(14.8)	(0.10)	(0.4)	(0.6)	(1.2)	(3.7)
After	79.8	37.1	52.8	0.811†			105.6					
extubation	(21.4)	(9.9)	(13.2)	(0.149)			(13.8)					

TABLE III. *Data in the enflurane group (mean (SD)). Vapour concentrations and type of ventilation are given in the first column.* FI_{enf}, FE_{enf} *= inspiratory and end-tidal concentrations of enflurane. For other abbreviations and significance indicators, see table II*

	*V*s,mca (cm s^{-1})	*V*d,mca (cm s^{-1})	*V*m,mca (cm s^{-1})	PI	FI_{enf} (%)	FE_{enf} (%)	MAP (mm Hg)	E'_{CO_2} (%)	Pv_{CO_2} (kPa)	*T*ns (°C)	Hb (g%)	PCV (%)
Awake	82.3	40.7	54.4	0.771			99.5					
	(18.2)	(9.7)	(11.0)	(0.100)			(10.5)					
After induction	63.2	24.7*	35.8*	1.090*			101.1					
	(15.4)	(7.4)	(9.2)	(0.225)			(16.4)					
1.7 vol%, normovent.	71.7	40.5†	51.1†	0.619†	1.42	0.99	85.1	5.02	5.3	36.0	13.0	38.9
	(15.9)	(9.8)	(12.1)	(0.147)	(0.08)	(0.09)	(17.7)	(0.15)	(0.4)	(0.3)	(1.9)	(5.8)
1.7 vol%, hypervent.	54.7*	29.4	38.8*	0.683	1.39	1.11	97.2	3.46	4.2	35.8	12.8	38.4
	(9.7)	(7.9)	(9.1)	(0.206)	(0.09)	(0.11)	(19.6)	(0.10)	(0.3)	(0.3)	(1.7)	(5.2)
3.4 vol%, normovent.	84.3†	51.9*†	63.3†	0.524*	2.96	2.01	98.5	5.09	5.3	35.8	13.0	38.9
	(20.7)	(15.8)	(16.3)	(0.105)	(0.15)	(0.18)	(17.5)	(0.12)	(0.4)	(0.3)	(2.0)	(5.9)
3.4 vol%, hypervent.	52.9*†	28.7†	37.5*†	0.662	2.84	2.29	88.2	3.41	4.1	35.7	13.4	39.4
	(8.5)	(6.0)	(6.9)	(0.168)	(0.15)	(0.21)	(18.2)	(0.10)	(0.5)	(0.4)	(1.5)	(5.4)
3.4 vol%, normovent., no N_2O	65.9	37.8	47.7	0.602	3.10	2.11	94.2	5.04	5.4	35.7	13.2	39.4
	(13.9)	(10.5)	(10.9)	(0.132)	(0.18)	(0.33)	(21.0)	(0.12)	(0.4)	(0.5)	(1.9)	(5.8)
After extubation	80.1	39.1	53.5	0.785			102.8					
	(19.0)	(11.5)	(13.7)	(0.156)			(16.2)					

TABLE IV. *Data in the isoflurane group (mean (SD)). Vapour concentrations and type of ventilation are given in the first column.* FI_{iso}, FE_{iso} *= inspiratory and end-tidal concentrations of isoflurane. For other abbreviations and significance indicators, see table II*

	*V*s,mca (cm s^{-1})	*V*d,mca (cm s^{-1})	*V*m,mca (cm s^{-1})	PI	FI_{iso} (%)	FE_{iso} (%)	MAP (mm Hg)	E'_{CO_2} (%)	Pv_{CO_2} (kPa)	*T*ns (°C)	Hb (g%)	PCV (%)
Awake	89.1	43.1	59.5	0.788			98.0					
	(20.0)	(11.2)	(13.6)	(0.200)			(12.8)					
After induction	67.4*	25.9*	39.6*	1.073			98.6					
	(16.8)	(8.8)	(9.9)	(0.300)			(18.7)					
1.2 vol%, normovent.	76.4	39.5	53.2	0.728	1.08	0.79	86.4	5.03	5.3	35.7	14.0	42.3
	(25.3)	(16.5)	(19.7)	(0.158)	(0.09)	(0.09)	(19.4)	(0.07)	(0.4)	(0.7)	(1.2)	(2.8)
1.2 vol%, hypervent.	55.8*†	26.0*	36.1*†	0.895	1.05	0.89	95.9	3.50	4.1	35.5	14.0	42.2
	(17.9)	(11.2)	(14.3)	(0.300)	(0.10)	(0.11)	(16.2)	(0.12)	(0.4)	(0.8)	(1.2)	(3.6)
2.4 vol%, normovent.	79.9†	38.6	54.0†	0.821	2.14	1.58	88.8	5.01	5.3	35.5	14.2	42.5
	(22.1)	(15.8)	(19.2)	(0.227)	(0.15)	(0.16)	(16.5)	(0.09)	(0.4)	(0.8)	(1.4)	(4.3)
2.4 vol%, hypervent.	48.9*†	15.3*†	25.8*†	1.972*†	2.06	1.74	86.7	3.47	4.0	35.4	14.3	42.9
	(18.5)	(13.6)	(16.4)	(1.400)	(0.15)	(0.15)	(12.4)	(0.08)	(0.4)	(0.8)	(1.6)	(4.6)
2.4 vol%, normovent., no N_2O	69.4*†	36.4†	49.0†	0.698†	2.38	1.63	98.8	5.00	5.5	35.5	14.5	43.3
	(24.6)	(14.7)	(19.2)	(0.164)	(0.20)	(0.30)	(14.5)	(0.07)	(0.5)	(0.8)	(1.5)	(4.7)
After extubation	92.9†	45.3	62.6	0.774			105.4					
	(23.0)	(13.3)	(17.0)	(0.152)			(13.0)					

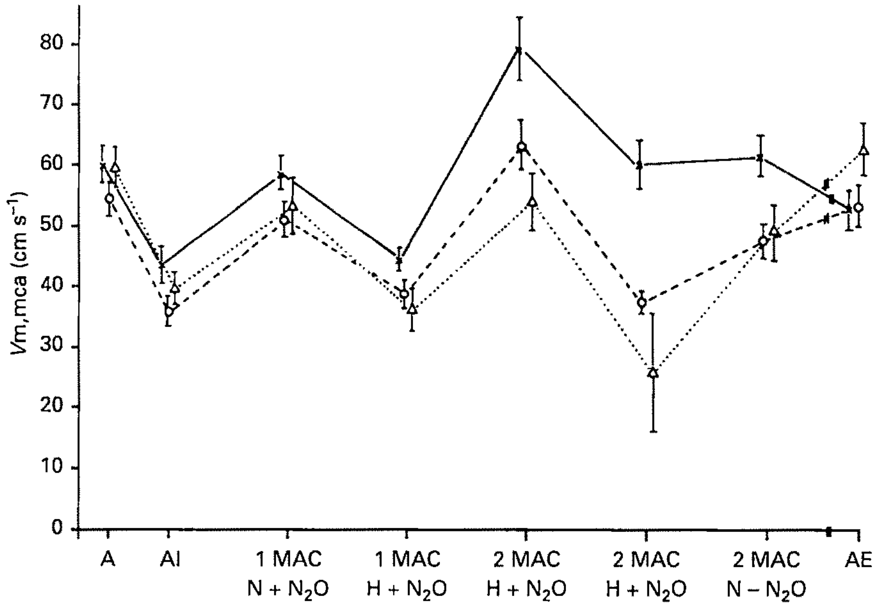

FIG. 1. Mean (SEM) changes in mean blood flow velocity in the middle cerebral artery (*V*m,mca). There are clear differences in *V*m between the groups after administration of 1.6% halothane (—), 3.4% enflurane (---) or 2.4% isoflurane (....) (2 MAC). *n* = 17 each group. A = Awake; AI = after intubation; N = normoventilation; H = hyperventilation; AE = after extubation.

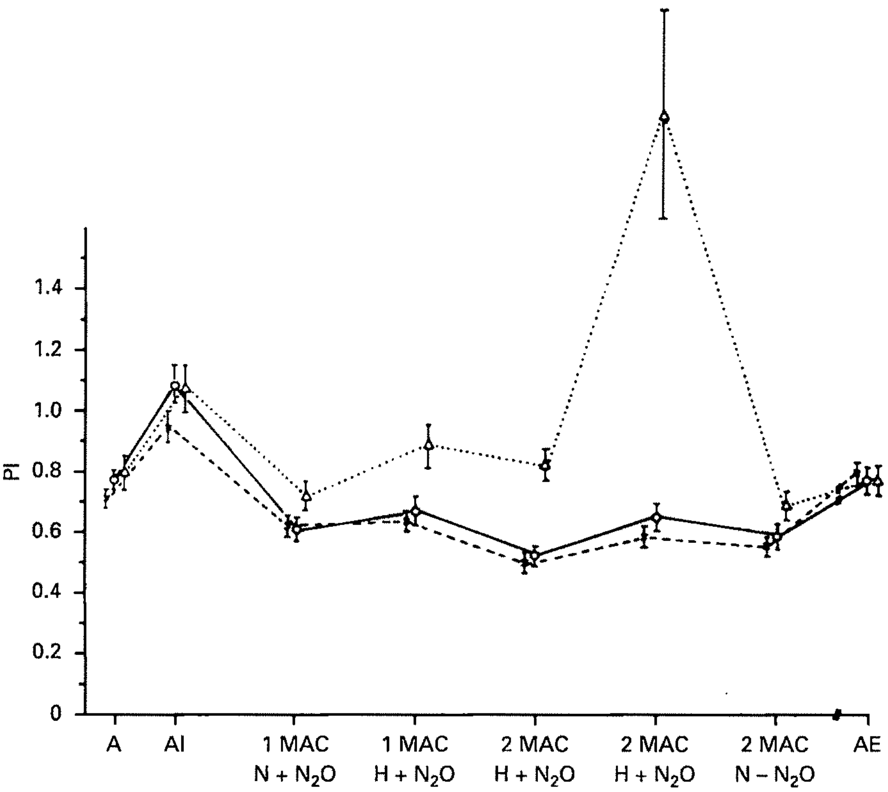

FIG. 2. Mean (SEM) changes in pulsatility (PI) in the TCD waveform (PI = (Vs − Vd)/Vm). Note the increase of PI in patients receiving 2 MAC (2.4 %) isoflurane (....), especially when hyperventilated in the presence of 66 % nitrous oxide in oxygen. Here six of 17 patients had a Vd,mca = 0 cm s^{-1}, thus explaining the striking SEM. --- = Halothane group; — = enflurane group. $n = 17$ each group. For other abbreviations, see figure 1.

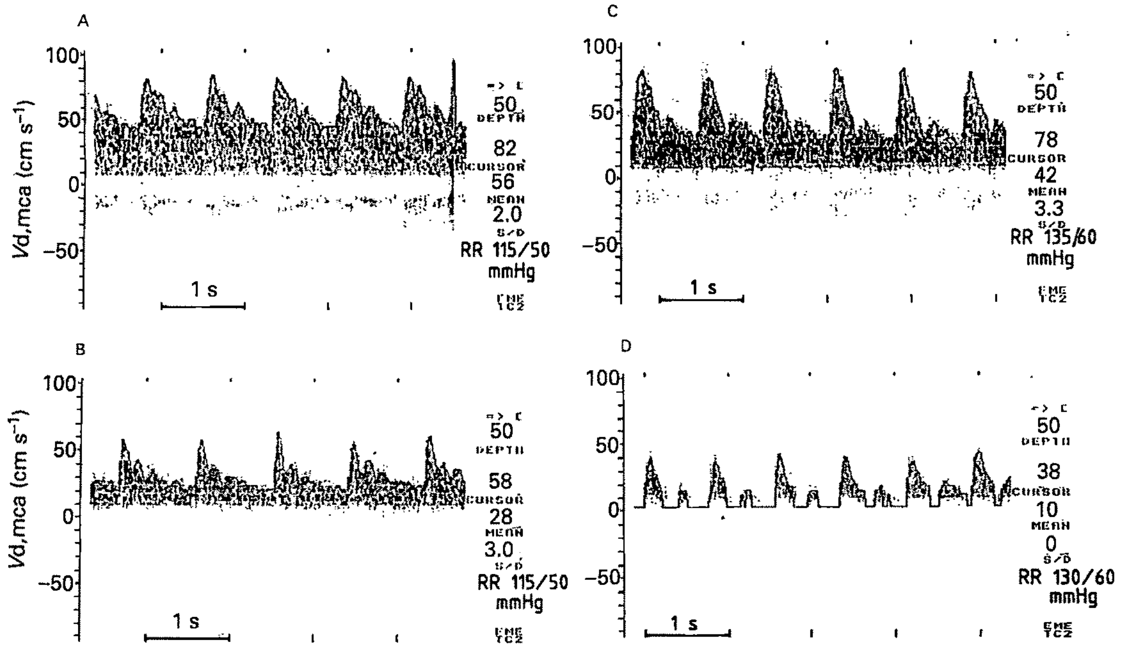

FIG. 3. TCD in a 25-yr-old patient given different inspired concentrations of isoflurane and nitrous oxide in oxygen under varying ventilatory conditions: A = 1.2 % isoflurane, normoventilation (E'_{CO_2} = 5.0 %); B = 1.2 % isoflurane, hyperventilation (E'_{CO_2} = 3.5 %); C = 2.4 % isoflurane, normoventilation; D = 2.4 % isoflurane, hyperventilation. Here, diastolic blood flow velocity (Vd,mca) is decreased to 0 cm s^{-1}.

thiopentone 5–6 mg kg^{-1}, Vm,mca decreased significantly with increases in pulsatility. With small doses of halothane (0.8 %), enflurane (1.7 %) and isoflurane (1.2 %) in nitrous oxide in oxygen and normoventilation, TCD variables did not differ significantly from awake values. Hyperventilation caused clear decreases in MCA flow velocities in all groups, whereas pulsatility varied inconsistently.

After the concentrations of the anaesthetic agents were increased, there were obvious differences in TCD variables between the three groups. Compared with the awake state, patients receiving 1.6 %

halothane and nitrous oxide in oxygen during normoventilation showed significant increases in MCA blood flow velocities. In contrast, there were only minor changes when 3.4% enflurane or 2.4% isoflurane was given. Pulsatility decreased significantly in patients receiving halothane or enflurane, whereas slight increases were observed in the isoflurane group.

Compared with these data, in all groups hyperventilation was associated with decreases in MCA flow velocities and increases in pulsatility, the latter being most pronounced in the isoflurane group, where Vd,mca was 0 cm s^{-1} in six of 17 patients (fig. 3).

MCA blood flow velocities decreased in all groups when nitrous oxide was replaced by oxygen (normoventilation, high concentrations of halogenated agents), but the changes were significant only in the enflurane group.

Three-dimensional analysis of variance for repeated measures confirmed significant differences in Vm,mca and pulsatility between the groups ($P < 0.001$).

In all groups, mean arterial pressure did not change significantly during the study when compared to the awake values. Nasopharyngeal temperature decreased slightly during anaesthesia and surgery, without inter-group differences. There were minimal changes in haemoglobin concentration and PCV.

DISCUSSION

There is increasing interest in the intraoperative use of transcranial Doppler sonography, especially during cardiovascular procedures [4–8].

Provided that the diameters of the basal cerebral arteries remain constant under varying conditions [15], cerebral blood flow velocity should change proportionally with cerebral blood flow (CBF). In a TCD validation study [3], such close relations between blood flow velocities in the middle cerebral artery and CBF were confirmed in symptomatic patients with cerebrovascular diseases. In contrast to CBF methods, TCD allows *continuous* non-invasive monitoring of cerebral haemodynamics.

When TCD is used during operation, the effects of anaesthetic agents have to be considered, as CBF may be influenced by the anaesthetic regimen. Schregel, Beverungen and Cunitz [10] found an increase in MCA flow velocities during halothane anaesthesia (mean inspired concentration 0.8–0.95%), whereas only minor changes occurred when fentanyl and droperidol were used. In hydrocephalic patients receiving 1.0% ($n = 12$) or 2.0% ($n = 5$) isoflurane, Lundar and associates [11] found no significant changes in MCA flow velocity. There are no TCD data on the effects of enflurane or nitrous oxide. Controlled ventilation using a positive end-expiratory pressure > 10 cm H_2O may decrease MCA flow velocity [16].

In the present study, marked decreases in MCA blood flow velocity and increases in pulsatility were observed after induction of anaesthesia with thiopentone 5–6 mg kg^{-1}. This is consistent with previous reports on the effects of barbiturates on TCD variables [12, 13] and may mirror their known cerebral vasoconstrictor properties [9].

It is held generally that CBF increases to different extents after administration of halothane, enflurane or isoflurane; cerebral vasodilatation is greatest with halothane, less with enflurane and least with isoflurane [9]. In our study, similar changes in cerebral blood flow velocities occurred with increasing concentrations of the three agents. With normoventilation in nitrous oxide in oxygen, Vm,mca increased in the halothane group, but only slight variations were observed after enflurane or isoflurane.

The concentrations of the three agents were chosen as approximately equipotent. Regardless of the anaesthetic concentration, in all patients MCA flow velocities were smaller and pulsatility was greater after hyperventilation ($E'_{CO_2} = 3.5\%$) compared with normoventilation ($E'_{CO_2} = 5.0\%$). This suggests that cerebral carbon dioxide reactivity was preserved with large doses of halothane, enflurane and isoflurane.

In six of 17 patients receiving isoflurane, diastolic MCA blood flow velocity was zero with 2.4% isoflurane and nitrous oxide in oxygen and hyperventilation. This phenomenon (Vd,mca = 0 cm s^{-1} (table IV)) was not observed with normoventilation or in any patient given halothane or enflurane. Thus some additional comment is necessary.

First, a marked increase in intracranial pressure (ICP) may decrease diastolic MCA flow velocity to 0 cm s^{-1} [17]. Isoflurane may increase ICP, especially when used in large concentrations [18]. If the observed loss of diastolic MCA flow velocity were caused by an increased ICP, one would expect this phenomenon to occur during normoventilation, rather than hyperventilation.

Second, it has been suggested that the diameters of the basal cerebral arteries do not remain constant during general anaesthesia [13]. This would produce considerable changes in blood flow velocities as determined by TCD, and obvious differences between flow velocity and CBF.

Third, cortical CBF was found to decrease in hypocapnic rabbits with 1 MAC isoflurane, whereas 1 MAC halothane increased CBF regardless of the Pa_{CO_2} [19]. However, it is difficult to compare our TCD data with these findings because of species and methodological differences.

In the presence of large concentrations of volatile anaesthetic agents and normoventilation, we found greater MCA blood flow velocities during administration of nitrous oxide than after its withdrawal. The difference was significant only in the enflurane group. This may be explained by cerebral vasodilatation caused by nitrous oxide. Animal studies have demonstrated significant increases in CBF when nitrous oxide was added to halothane or isoflurane anaesthesia [19, 20].

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British Journal of Anaesthesia 1992; **68**: 394–397

RAPID ADMINISTRATION OF CRYSTALLOID PRELOAD DOES NOT DECREASE THE INCIDENCE OF HYPOTENSION AFTER SPINAL ANAESTHESIA FOR ELECTIVE CAESAREAN SECTION

C. C. ROUT, S. S. AKOOJEE, D. A. ROCKE AND E. GOUWS

SUMMARY

Twenty parturients undergoing elective Caesarean section were allocated randomly to receive crystalloid preload 20 ml kg^{-1} *over either 20 min or 10 min before spinal anaesthesia. Significant hypotension (systolic arterial pressure* < 100 *mm Hg and* $< 80\%$ *of baseline value) occurred in six of the 10 patients in the 20-min preload group and seven of 10 patients in the 10-min preload group (ns). Both groups had a significant (*$P < 0.05$*) increase in central venous pressure during the preload period. The mean central venous pressure in the 10-min group was 11.9 mm Hg (range 6–19 mm Hg), which was significantly greater (*$P < 0.05$*) than that in the 20-min group (mean 7.3 mm Hg, range 2–13 mm Hg). Three patients in the 10-min group had clinically unacceptable increases in central venous pressure. This study has demonstrated that rapid administration of crystalloid preload before spinal anaesthesia did not decrease the incidence or severity of hypotension, and questions the role of crystalloid preload.*

KEY WORDS

Anaesthesia: obstetric. Anaesthetic techniques: spinal. Complications: hypotension. Fluid balance: fluid therapy.

Hypotension associated with spinal anaesthesia for Caesarean section remains a serious and common complication, despite several measures used to reduce both incidence and severity. The cornerstones of prevention are the use of a left lateral tilt and volume preloading. In our institution, preloading is undertaken with crystalloid solution 20 ml kg^{-1} administered over 20 min before subarachnoid injection. This regimen may still fail to prevent hypotension, possibly because of redistribution of crystalloid from the intravascular compartment. This study has investigated if a shorter period of preloading would reduce the incidence and severity of hypotension without adverse maternal and neonatal effects.

PATIENTS AND METHODS

The study was approved by the Professional and Ethical Standards Committee of the Faculty of Medicine, University of Natal. Informed consent was obtained from 20 healthy parturients undergoing elective Caesarean section. Patients with medical or obstetric complications or evidence of impaired placental function were excluded. All patients were at term (38–41 weeks gestation), had singleton pregnancies with cephalic presentations and did not weigh more than 90 kg. Patients were transported to the theatre in the full lateral position and received 30 ml of sodium citrate 0.3 mol litre^{-1} after entry to the theatre.

A 14-gauge peripheral i.v. cannula and a 16-gauge central venous pressure (CVP) catheter were inserted under local anaesthesia in the left forearm and antecubital fossa, respectively. The location of the tip of the CVP line was confirmed by transduced waveform. The cuff of an automated non-invasive arterial pressure monitor (Critikon Dinamap) was applied to the patient's right arm. With the patient comfortably at rest in the left supine wedged position, baseline arterial pressure, heart rate and CVP were obtained. Baseline heart rate and arterial pressure were taken as the mean of three consecutive readings at 3-min intervals during which the systolic pressure did not vary by more than 10% from its average value. The zero point for the CVP was taken as the fourth intercostal space in the anterior axillary line.

After baseline recordings the patient was positioned on the operating table. To allow spinal injection at the exact conclusion of the preload period, the patient was placed in the full left lateral position with the legs flexed. Another set of baseline values were obtained in this position before the fluid preload was started. Patients were then allocated randomly to receive crystalloid preload 20 ml kg^{-1} (Plasmalyte-L) over either 20 min (group 1) or 10 min (group 2) immediately before spinal anaesthesia. To ensure consistency between patients during the preloading period, the zero point for the CVP was taken as the midline at the level of the sixth thoracic vertebra. After these further readings, preloading was commenced and timed with a stopwatch. In group 2, a high flow i.v. administration set was required in order to administer the 20 ml kg^{-1} over 10 min. Haemodynamic variables were recorded at 5-min intervals during the preloading period. At the conclusion of the preloading

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TABLE I. *Group data (mean (range or* SD)*). *Parity not known for one patient in group 2. ID = Subarachnoid injection–delivery interval; UD = uterine incision–delivery interval*

	Group 1 20-min preload	Group 2 10-min preload
Age (yr)	25.4 (21–29)	28.6 (23–37)
Weight (kg)	68.8 (8.28)	68.4 (8.05)
Parity*	2.2 (1.03)	2.4 (1.94)
Thoracic sensory level at 5 min	3.7 (1.06)	3.6 (0.70)
ID time (min)	20.3 (11.48)	18.5 (3.78)
UD time (s)	53.9 (25.74)	70 (48.63)
Preload (ml)	1390 (180.74)	1390 (171.92)
Total volume (ml)	1720 (278.09)	1795 (296.69)
Baseline		
Systolic pressure (mm Hg)	121.9 (7.58)	117.9 (11.05)
Diastolic pressure (mm Hg)	66.9 (7.41)	66.8 (11.59)
Heart rate (beat min^{-1})	84.2 (14.12)	89.3 (14.58)
CVP (mm Hg)	0.7 (1.49)	−0.1 (2.85)

period, 0.5% plain bupivacaine 1.5 ml was injected via a 25-gauge spinal needle at the L4–5 interspace. The patient was returned promptly to the left supine wedged position and arterial pressure and heart rate recorded at 1-min intervals for 10 min and at 5-min intervals thereafter.

Hypotension was defined as a decrease in systolic pressure to both less than 100 mm Hg *and* 80% of baseline value. Hypotension was treated by increased rate of fluid infusion and incremental i.v. bolus doses of ephedrine 5 mg at 1-min intervals until the pressure had returned to within 20% of baseline value or greater than 100 mm Hg. All patients received 40% oxygen by mask after the spinal injection and an oxytocin infusion after delivery.

Neonatal condition was assessed by modified Apgar score (Apgar minus colour) at 2 and 5 min after delivery and by umbilical venous and arterial blood-gas and acid–base analysis of samples obtained from an isolated, double-clamped segment of umbilical cord. A sample of maternal radial arterial blood was obtained between uterine incision and delivery. The times of spinal injection, uterine incision and delivery (first clamping of cord) were recorded.

The haemodynamic data, collected in a repeated measures experimental design, were analysed statistically with the appropriate analysis of variance testing for differences between groups and for changes within groups. The groups were compared with respect to patient data and blood-gas variables using Student's unpaired *t*-test; the Mann–Whitney *U* test was used where appropriate for non-parametric data.

RESULTS

There were 10 patients in each group (table I). There were no significant differences between the two groups.

There was no significant change in the mean baseline CVP values when the patient was moved from the left supine wedged position to the full lateral position (0.7 (SD 1.49) mm Hg to 1.1 (2.47) mm Hg in the 20-min group and −0.1 (2.85) mm Hg to 0.3 (2.21) mm Hg in the 10-min group). Both groups showed a significant ($P < 0.05$) increase in CVP during the preload period (fig. 1). The mean CVP after fluid administration in those patients receiving the fluid over 10 min was 11.9 mm Hg (range 6–19 mm Hg), which was significantly greater ($P < 0.05$) than in those patients receiving the same volume over 20 min (mean 7.3 mm Hg, range 2–13 mm Hg). Heart rate increased from a mean of 84.8

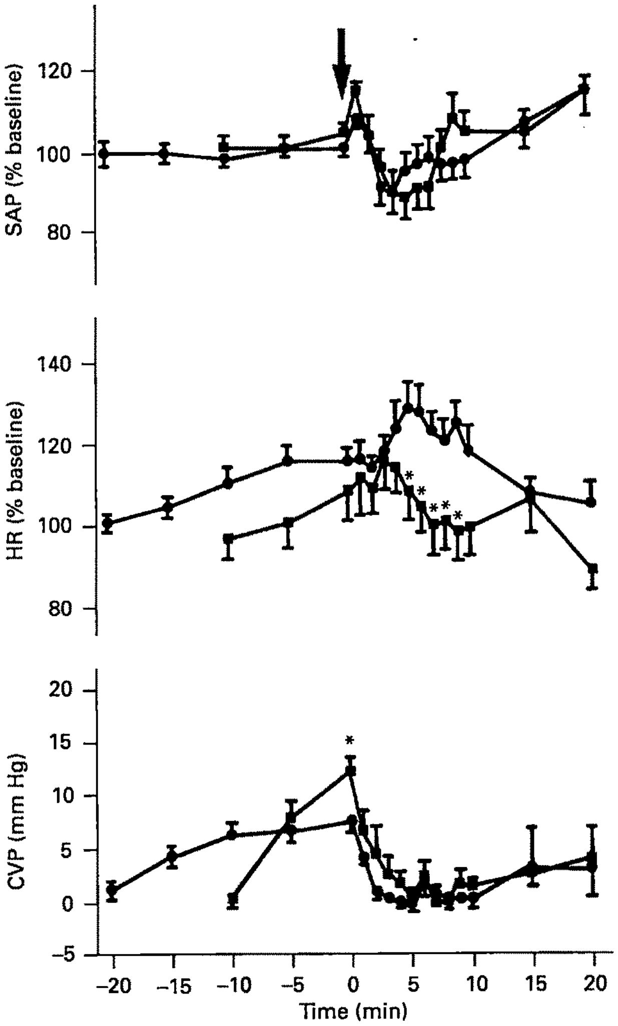

FIG. 1. Changes in systolic pressure (SAP) and heart rate (HR) (percentage of baseline value) and central venous pressure (CVP) (mean, SEM) during crystalloid preload administered over 10 min (■) or 20 min (●) before spinal anaesthesia. Arrow indicates time of spinal injection of bupivacaine. * $P < 0.05$ between groups.

(13.32) beat min^{-1} to 95.9 (12.10) beat min^{-1} in the patients receiving preload over 20 min ($P < 0.01$), and from 85.3 (10.76) beat min^{-1} to 94.7 (16.03) beat min^{-1} in patients receiving preload over 10 min. There were no significant changes in arterial pressure during the preloading period.

It was not possible to obtain accurate CVP values from all subjects at all times following spinal injection, because of patient movement and surgical interference. However, sufficient data sets were available to permit a repeated measures analysis of the first 10 min. Mean CVP decreased rapidly in both groups. There was no significant difference between groups or between subjects in the behaviour of CVP with time, but there was a highly significant ($P = 0.0002$) within-subject effect. CVP values were significantly less ($P < 0.01$) than the value after preload at all times from 1 to 10 min after spinal injection. There was no significant difference between the groups at any time.

Seven patients in the 10-min group developed hypotension severe enough to require ephedrine, compared with six patients in the control group. The duration of hypotension, and thus dose requirement of ephedrine, was less in the 10-min group than in the 20-min group, but this was not statistically significant. Mean ephedrine requirement was 9.3 (5.34) mg in the 10-min group and 15.8 (10.68) mg in the 20-min group ($P = 0.18$).

There were no significant differences in systolic pressure after spinal injection between the groups (fig. 1). There was a significant ($P = 0.002$) change in group average systolic pressures with time in both groups, with a significant ($P = 0.0001$) increase at 1 min and significant decreases at 4 min ($P = 0.01$), 5 min ($P = 0.004$) and 6 min ($P = 0.05$). Group average systolic pressure decreased to a minimum of 108 (19.9) mm Hg at 4 min and 103 (23.6) mm Hg at 5 min in the 20-min and 10-min groups, respectively.

Each group showed a significant increase in heart rate compared with baseline values after spinal injection (fig. 1). However, heart rate returned to baseline values much more rapidly in patients who had received their preload over 10 min. This group had significant increases in heart rate from 1 to 4 min, whereas the group of patients receiving their preload over 20 min had significantly increased mean heart rates from 1 to 10 min. Percentage change in mean heart rates in the two groups were significantly ($P < 0.05$) different at 5–9 min after spinal injection.

All the neonates were in good condition at delivery with maximum Apgar (A – C) scores at 2 and 5 min, with the exception of one neonate in the 10-min preload group who scored 7 at 2 min. Delivery of this infant was delayed because of surgical difficulties (U–D time 195 s).

There were no significant differences in maternal arterial blood-gas and acid–base state between the two groups. Umbilical venous and arterial samples were obtained in all but two subjects, one in each group. In one, in the 10-min group, the umbilical cord clamps were removed on the operating table and in one in the 20-min group there was insufficient umbilical arterial blood to sample. There were no significant differences between the groups.

DISCUSSION

This study has demonstrated that rapid infusion of crystalloid preload 20 ml kg^{-1} over 10 min did not reduce the incidence of hypotension after spinal anaesthesia for Caesarean section, compared with the same volume infused over 20 min, despite the significantly greater central venous pressures demonstrated immediately before spinal injection. Whilst the severity of hypotension was similar in both groups, the duration of hypotension and ephedrine dose requirement were greater in the 20-min group. Although this difference did not achieve statistical significance, the number of patients studied was small, and a true difference cannot be excluded.

The increase in CVP achieved after infusion over 20 min in our study is comparable to that produced by Wollman and Marx, who infused 1000 ml over 14–20 min [1]. They concluded that rapid infusion of crystalloid solutions was safe in parturients with no cardiovascular compromise. Whilst the mean CVP achieved after preload in the 10-min group was within clinically acceptable ranges, three patients had values which caused concern (16, 19 and 19 mm Hg). In 1966, Askrog was unable to demonstrate any untoward effects of infusing 1000 ml over 4 min and only a transient increase in pulmonary artery pressure, although his subjects were receiving halothane anaesthesia and were not pregnant [2]. There is evidence to suggest that parturients might be more susceptible to pulmonary oedema after rapid administration of crystalloid solutions, possibly because of an increase in lung water during pregnancy with a reduced pulmonary interstitial safety margin [3]. In addition, Wennberg and colleagues compared crystalloid administration with colloid during the onset of extradural anaesthesia and demonstrated more pronounced increase in thoracic fluid index, indicative of thoracic fluid accumulation, after crystalloid than after colloid administration [4]. They also demonstrated a significant difference in colloid osmotic pressure between the two groups.

One reason why rapid crystalloid preloading did not significantly reduce the incidence of post-spinal hypotension, despite the high CVP values observed, might be the rapid loss of fluid into the lungs. If this were the case, it is possible that colloidal solution might be more effective. Mathru and co-workers [5] compared 15 ml kg^{-1} of colloid-containing solution with the same volume of crystalloid solution administered over 15–20 min before spinal anaesthesia for elective Caesarean section. They reported a zero incidence of hypotension following spinal anaesthesia in patients receiving albumin, compared with a 33% incidence in patients receiving crystalloid. However, this has not been supported by comparisons of colloid with crystalloid preload before extradural anaesthesia [6, 7]. Also, if fluid transfer to the lungs was significant in our study, this was not reflected by a difference in maternal arterial oxygen tensions (23.5 (2.70) kPa and 21.2 (4.60) kPa in the 20-min and 10-min groups, respectively).

An alternative explanation of our results is that volume preloading has only a limited role in the prevention of post-spinal hypotension. The early evidence for the use of volume preloading before spinal anaesthesia for Caesarean section comes from studies performed before lateral uterine displacement was routine practice or where the initial diagnosis of hypotension was made before uterine displacement. In a study examining the effects of volume preloading and uterine displacement Clarke, Thompson and Thompson [8] demonstrated a significant reduction in the incidence of post-spinal hypotension after volume preloading (from 92% to 57%) in patients not in labour. However, the incidences of hypotension requiring ephedrine following left lateral tilt were 48% (no preload) and 42% (preload) (ns).

The rapid decrease in mean CVP values in both groups after spinal anaesthesia confirms that a decrease in venous return is relevant to the aetiology of post-spinal hypotension. However, the rapidity of onset of hypotension and the severity of the decrease in CVP (despite preloading) suggest that fluid therapy during the onset of sympathetic block is not a practical method of preventing hypotension, as sufficient volume cannot be administered in the time available. Alternative methods of increasing venous return, such as leg elevation and leg wrapping after spinal injection may be more successful [9].

In 1989 Murray, Morgan and Whitwam summarized the literature which showed that, with few exceptions, preloading did not eliminate hypotension, which remained as much as 52.8% in one paper [6]. Our study supports this and, in addition, demonstrates that rapid administration of preload did not reduce the incidence of hypotension, leading us to question the value of crystalloid preload in the prevention of hypotension.

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REVIEW ARTICLE

ANAESTHESIA AND THE VENTILATORY SYSTEM IN INFANTS AND YOUNG CHILDREN

D. HATCH AND M. FLETCHER

It is not possible in a single review article to cover all aspects of anaesthesia and the respiratory system in infants and young children. We shall concentrate, therefore, on those matters which are of particular relevance to the anaesthetist, and those in which there have been recent developments. We are also aware of the increasing numbers of ex-premature infants presenting for surgery, who appear to be particularly vulnerable to the adverse effects of general anaesthesia.

The increased susceptibility of infants and young children to respiratory infection is well documented and results in part from the limited respiratory reserve in this age group. Oxygen consumption is high, decreasing gradually from around 7 ml kg^{-1} min^{-1} at birth to the adult value of 3–4 ml kg^{-1} min^{-1}. The outward recoil of the chest wall in infants and young children is low (the pressure–volume curve is shifted), although the inward recoil of the lungs is similar to that of the young adult [2, 33, 109]. Negative intrathoracic pressure, upon which the patency of small airways mainly depends, is less negative in absolute terms so that, assuming the vertical pleural pressure gradient down the lung remains unchanged, the tendency to airway closure during tidal breathing may increase [59]. As functional residual capacity (FRC) is the lung volume at which the outward recoil of the chest wall exactly balances the inward recoil of the lungs (fig. 1), the shift of the pressure–volume curve of the chest wall without corresponding change in lung recoil leads to a reduction in FRC unless it is maintained by other mechanisms [61]. There is evidence that mechanisms such as laryngeal braking during expiration and active diaphragmatic and intercostal expiratory tone may have roles in maintenance of lung volume in the awake state, although not necessarily during anaesthesia [62, 63, 136].

The geometry of the rib cage changes during the first 2 years of life, with the gradual development of the "bucket handle" configuration of the ribs seen in adult life (fig. 2) [106]. The more horizontal configuration of the infant's rib cage limits the potential for thoracic expansion. In addition, the "ventilatory pump" (rib cage, diaphragm, abdominal and accessory muscles) is thought to be less efficient in young children because of instability of the chest wall and liability of the diaphragm to fatigue as a result of the relative paucity of type I muscle fibres.

All these factors increase the susceptibility of infants, not only to respiratory infection, but also to

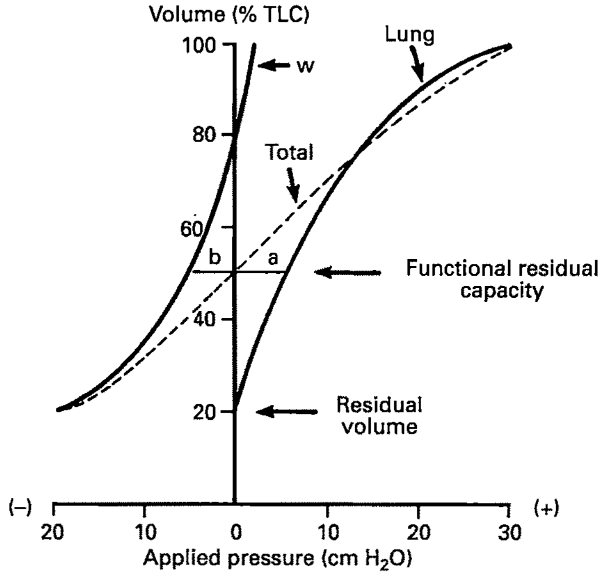

FIG. 1. Deflation pressure–volume curves for the lung, chest wall (w) and total ventilatory system (interrupted line). Note that at functional residual capacity, the outward recoil tendency of the chest wall (point b) exactly balances the tendency of the lung to collapse (point a). TLC = Total lung capacity. (From Taylor and colleagues [133].)

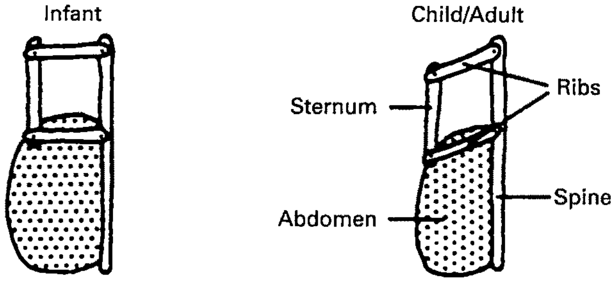

FIG. 2. Changes in rib cage configuration from infancy to early childhood (From Openshaw, Edwards and Helms [106].)

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TABLE I. *Effects of inhalation anaesthetic agents on ventilation in children. H = Halothane; I = isoflurane; E = enflurane.* † *"Sparing effect" on ventilation compared with isoflurane*

					Effect of agent on			
Author	Agent	Opioid premed?	No. of subjects	Age or wt range	f	V_T	$P_{E'CO_2}$	Response to CO_2
Larsson [77]	H	No	39	15–300 days			↑	
Olsson [104]	H	No	13	1 day– 5 months	↑	↓	↑	Intact
Murat [100]	H	No	12	20–68 months	↑	↓	↑	
Murat [101]	I	No	13	13–75 months	↑	↓	↑	
	N_2O†							
Johannesson [68]	H	Yes	8	12–24.5 kg	↑	↓	↑	
	E	Yes	8	13.7–24 kg	↓	↓	↑↑	
	I	Yes	8	10.7–26.5 kg	↑	↓	↑	
O'Neill [105]	H	Yes	20	5–14 yr	0	↓	↑	
	E	Yes	20	5–14 yr	↓	↓	↑↑	
Wren [150]	H	No	8	5–10 yr	↑	↓	↑	
	I	No	8	5–9 yr	0	↓	↑	
	E	No	8	5–9 yr	0	↓	↑↑	
Murat [99]	H	No	10	1–6 yr	↑	↓	↑	↓
	I	No	10	1–6 yr	0	↓	↑	↓
	E	No	9	1–6 yr	↓	↓	↑	↓
Lindahl [85]	H	Yes	10	1–11 yr	↑	↓	↑	
Wren [149]	N_2O	Yes	6	7–12 yr	0	0	0	

the adverse ventilatory effects of anaesthesia. These adverse effects, although well documented in adults, have been more difficult to study in infants and young children. In particular there is little information in the literature about the rate of maturation of ventilatory function in the early years of life. Ethical and technical considerations in infants and children, together with the inability of young children to understand the concept of maximal voluntary effort make it particularly difficult to undertake research in this age group. The relatively small number of patients studied over a wide age range in some studies may have masked important age-dependent effects.

EFFECTS OF ANAESTHESIA ON VENTILATION

All three of the currently used inhalation anaesthetic agents, halothane, isoflurane and enflurane have a dose-dependent depressant effect on ventilation (table I). Reductions in tidal volume (V_T) to as little as 4 ml kg^{-1} and increases in end-tidal carbon dioxide tension ($P_{E'CO_2}$) to 8 kPa have been demonstrated in unpremedicated infants during halothane anaesthesia with spontaneous ventilation, with the greatest $P_{E'CO_2}$ values being seen in the youngest infants [77, 104]. Although $P_{E'CO_2}$ has been shown to correlate well with arterial carbon dioxide tension in children with normal lungs [84], the above studies are difficult to interpret, as V_T and $P_{E'CO_2}$ were not compared before and after induction of anaesthesia. The children studied appeared to tolerate increased carbon dioxide tensions without clinical problems, although this might not be the case for children with derangements in cardiorespiratory function. In unpremedicated older children, Murat and colleagues also found a reduction in spontaneous alveolar ventilation during anaesthesia [100].

Several workers have compared the effects of halothane, isoflurane and enflurane on respiration in children [68, 99, 105, 150]. The increase in $P_{E'CO_2}$ is probably not significantly different between these agents, although some studies are difficult to evaluate because of differences in premedication and induction agent. These agents do differ, however, in their effects on ventilatory frequency, halothane causing an increase, enflurane a reduction and isoflurane little change. The increase in ventilatory frequency with halothane results from a reduction in both inspiratory and expiratory time (T_I and T_E), the reverse changes occurring with enflurane. Studies in anaesthetized dogs have suggested that T_I is longer with enflurane than with halothane because of a different effect of the two agents on the bulbopontine "pacemaker" mechanism and not because of different effects on the phasic vagal inspiratory inhibitory mechanism [90]. Although isoflurane appears to have a limited effect on ventilatory frequency, a reduction in T_I can be demonstrated during its use [99].

Nitrous oxide does not produce significant depression of ventilation in children [149, 152]. Indeed, in unpremedicated young children (age range 13–75 months) the combination of nitrous oxide and isoflurane has a slight "sparing effect", with less reduction in tidal volume than an equal MAC

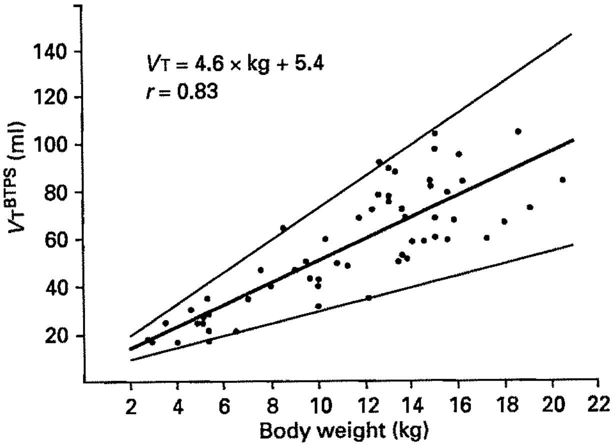

FIG. 3. Relationship of tidal volume to body weight showing regression line and 2SD. (From Lindahl, Hulse and Hatch [82].)

fraction of isoflurane alone [101]. The mechanism involved appears to differ from that reported in adults [35, 44].

Response to carbon dioxide

The ventilatory response to carbon dioxide is reduced in a dose-related manner by inhalation anaesthesia in infants and children, with no significant differences in the depression of the slopes of the carbon dioxide response curves between halothane, enflurane and isoflurane [85, 99, 104, 136]. During halothane anaesthesia at inspired concentrations of up to 1 %, unpremedicated infants appear able to maintain an unchanged PE'_{CO_2} in response to short periods of breathing 4 % carbon dioxide, but at greater inspired concentrations of halothane, PE'_{CO_2} increases. Although this depression in ventilatory response to carbon dioxide generally has been attributed to depression of the respiratory neurones in the medullary centre, Tusiewicz, Bryan and Froese have shown that, in children, a major component results from the preferential suppression of intercostal muscle activity [136]. Although attempts have been made to assess "central drive" by measurement of the pressure generated at the airway during brief periods of occlusion ($P_{0.1}$), this measurement cannot be used to quantitate respiratory centre output when there is instability of the chest wall. Indrawing of the chest wall muscles leads to errors that vary both with diaphragmatic drive and anaesthetic concentration.

Carbon dioxide output has been noted to be greater in children anaesthetized with halothane than in those anaesthetized with enflurane or isoflurane, possibly as a result of the greater concentrations of catecholamines reported with this agent [69, 71, 83].

Response to hypoxia

In the first few days of life, developmental changes occur in the ventilatory response to hypoxia [145, 146]. Both neonatal animals and humans at birth show a biphasic response, with initial increase in ventilatory drive being replaced by depression. This is replaced only gradually by the sustained increase in ventilation seen in the more mature subject. This maturation of response, which may also be affected by gestational age, may be related to changes in the sensitivity of the chemoreceptors after birth [89]. The effect of general anaesthesia on the response to hypoxia in the newborn neonate is uncertain. Small concentrations of volatile agents depress the response in adults and may have important implications in relation to postoperative apnoea in infants [73].

Effects of premedication

There appear to be few attempts in the literature to distinguish between the effects of premedicant drugs and anaesthetic agents on ventilatory function. In one study, premedication appeared to have little effect on tidal volume (fig. 3), which correlated well with body weight ($r = 0.83$) [82]. Non-opioid premedication (midazolam) has been shown to cause less depression of ventilatory frequency and minute ventilation than opioids, although without significant difference in PE'_{CO_2} [24]. Sedation with triclofos sodium, a derivative of chloral hydrate, causes a small increase in ventilatory frequency, but no significant change in oxygen saturation in infants and young children [67].

Local analgesic block

The combination of opioid premedication, inhalation anaesthesia with spontaneous breathing and removal of the surgical stimulus by effective local or regional block might be expected to cause respiratory depression. In one study, patients with effective caudal extradural block did have significantly smaller minute volumes and ventilatory frequencies than a similar group without caudal block, but without evidence of significant retention of carbon dioxide. It is likely that the group given caudal blocks received smaller concentrations of anaesthetic in this study, although this was not recorded. At the light levels of anaesthesia made possible by the use of caudal extradural block, no differences in PE'_{CO_2} during carbon dioxide-free breathing or in the ventilatory response to inhalation of 1.5 % carbon dioxide are seen between children receiving halothane and enflurane [22].

Laryngeal irritability

It is a well observed clinical fact that laryngeal irritability during anaesthesia is more pronounced in children than in adults, and may lead to serious hypoxaemia. Although Wren and colleagues found isoflurane was well accepted for inhalation induction in children, with a rapid induction time [151], the majority of studies have found it to be more irritant than halothane, particularly in unpremedicated children, with an increased incidence of laryngospasm, salivation, coughing and breath-holding [19, 38, 40, 88, 107].

Effects of i.v. anaesthetics

Although it has been shown that babies born by Caesarean section to women in whom anaesthesia has been induced with propofol have lower Apgar scores than those in whom thiopentone has been used, there are few published data on the effects of i.v. anaesthetic agents on the respiratory system in children [21]. With the possibly increasing use of total i.v. anaesthetic techniques and increased interest in the use of propofol infusions, there is a need for more studies in this area.

Effects of breathing systems

Deadspace and resistance of breathing systems are more critical during spontaneous breathing than during intermittent positive pressure ventilation (IPPV), when the main effect of using a high-resistance breathing system is to increase lung volume. The ventilatory responses of spontaneously breathing infants and young children to the addition of carbon dioxide to the inspired gas [80, 81], increased deadspace [23] and the addition of resistive loads [81] are well known. Although ventilatory compensation occurs rapidly at light levels of anaesthesia, increased work of breathing may result. The ventilatory compensation for added deadspace has been shown to be incomplete in some pre-term infants [137]. The effect of anaesthesia on respiratory muscle fatigue in infants and young children requires further study.

In 1937, Ayre noted that when infants breathed through a closed circuit their breathing became rapid, with "sighing" respirations, and that a dramatic improvement occurred when his T-piece system was used [3]. Since then, several studies have evaluated paediatric breathing systems and ventilatory equipment. When the T-piece and Bain systems are used at small fresh gas flows (FGF), carbon dioxide-containing gas is not breathed until the latter part of inspiration [92, 147], and this may not affect alveolar ventilation. Using modern T-piece ventilators which use a separate force to inflate the lungs, FGF can be kept small enough to provide some degree of heat and moisture retention in the upper air passages without alveolar rebreathing [53]. It is particularly important to measure $P\text{E}'_{CO_2}$ continuously when these small flows are used.

Although the design of the first circle systems was unsatisfactory for young children [1, 122], more modern versions provide a satisfactory alternative to the T-piece with regard to impedance to air flow [26]. The possibility of valves failing to function during use has been greatly reduced in these newer circuits. Flow resistive characteristics of tracheal tubes and connectors also are of critical importance, especially for infants [20, 51], and may be greater *in vivo* than *in vitro* measurements suggest [153]. Ventilators designed for adults may be unsuitable for use in children. High resistance breathing systems within these machines are particularly harmful during weaning from ventilatory support [13].

It is beyond the scope of this article to review the detailed characteristics of ventilatory and anaesthetic equipment used in children, but excellent articles may be found in standard paediatric textbooks [37, 46, 123].

Contributions of rib cage and diaphragm to breathing

The relative contribution of rib cage and diaphragm to inspiratory effort have been studied extensively in neonates and young children during natural sleep and sedation. The percentage contribution of the rib cage increases gradually during infancy so that, by around 9 months of age, it is similar to that found in quietly breathing adults [62]. During quiet sleep the ventilatory response to carbon dioxide breathing appears to depend more on the rib cage than the diaphragm, and it has been postulated that such a response acts to preserve the diaphragm in its most efficient configuration [63]. This response of the rib cage is not maintained during active rapid eye movement (REM) sleep, and may be compromised also during inhalation anaesthesia.

Profound depression of the rib cage contribution to ventilation has been demonstrated in children during halothane anaesthesia [136]. In infants, contraction of the diaphragm may cause paradoxical inward movement of the highly deformable chest wall, setting a downward spiral of reduced ventilatory efficiency and increasing diaphragmatic fatigue. Although animal studies suggest that, during quiet breathing, the diaphragm possesses considerable reserves of contractile force [121], infants have been shown to have fewer type I oxidative muscle fibres in the diaphragm than adults [72] and are thus theoretically more prone to develop ventilatory fatigue. Indeed, the work of breathing may be so great that assisted ventilation becomes a necessity [58].

During ventilation, expenditure of muscular energy is required to overcome the impedance of the respiratory system. Reduction in lung volume and compliance and increase in resistance occurring during anaesthesia are likely to result in an increase in work of breathing. Although this is usually clinically significant only during spontaneous breathing, increases in impedance may lead to underventilation when pressure generating lung ventilators are used.

Summary

All the currently used inhalation anaesthetic agents cause a dose-dependent depression of alveolar ventilation in infants and young children. There appears to be no evidence of significant differences in the degree of depression caused by each agent, although there are differences in their effects on ventilatory frequency.

Despite differences in respiratory physiology between infants and adults which are likely to predispose to underventilation in the very young, there is little evidence in the literature to suggest that general anaesthesia with spontaneous ventilation is necessarily harmful in infants with normal cardiopulmonary function. The use of supplementary local or regional analgesic techniques reduces the concentration of general anaesthetic required, and minimizes the risk of alveolar hypoventilation during spontaneous breathing.

EFFECTS OF ANAESTHESIA ON LUNG MECHANICS

Functional residual capacity

A reduction in FRC is well documented in recumbent adults on induction of either barbiturate or inhalation anaesthesia [56, 75, 114, 144], and the use of neuromuscular blocking agents does not seem

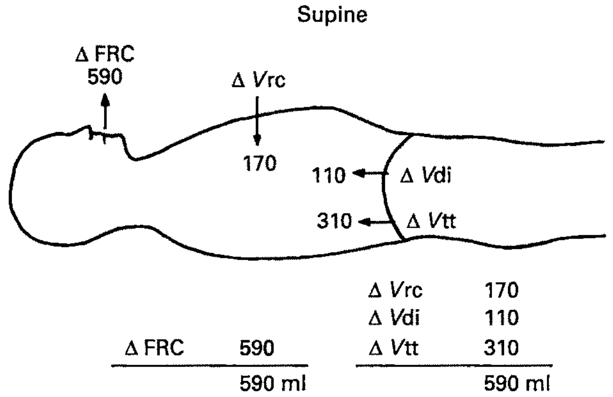

FIG. 4. Balance of volume (*V*) changes after induction of anaesthesia with muscle paralysis. rc = Rib cage; di = diaphragm; tt = thoracic tissue. (From Rehder [unpublished data].)

to lead to a further reduction [144]. Reduction in FRC has been documented also in infants and young children. Measurements made in one study during anaesthesia with muscle paralysis and controlled ventilation of the lungs in 14 children aged 6–18 yr revealed a mean reduction of 35% compared with values obtained previously in the awake supine state. In the six children younger than 11 yr in this study, the mean decrease in FRC was 44% [34]. More recent studies have failed to confirm decreases of this magnitude. In infants, the sleep state has been shown to affect FRC, with a possible reduction of 30% occurring during active REM sleep [61].

The mechanisms underlying this reduction in FRC are still not entirely clear. Changes in FRC could result from changes in the recoil forces of the chest wall or lung, cephalad movement of the diaphragm, from shifts in blood volume between the limbs, abdomen and thorax, or a combination of these factors [91]. Early studies in adults from the Mayo Clinic [113, 144] suggested that outward recoil of the chest wall is reduced after induction of anaesthesia with inhalation agents. Froese and Bryan, using cross table fluoroscopy, demonstrated cephalad displacement of the diaphragm on induction of anaesthesia in the supine position in two of three adult volunteers [47]. More recent studies have confirmed overall reductions in FRC of 500–600 ml with anaesthesia in healthy young adults, with reduction in thoracic rib cage volume accounting for between 150 and 300 ml of this reduction [56, 74]. Controversy exists, however, over the magnitude of diaphragmatic movement and shift in central blood volume on induction of anaesthesia. Hedenstierna and colleagues, using sequential computed tomographic scans, together with direct measurements of central blood volume in adult patients studied in the supine position, found a cephalad displacement of the diaphragm which would be estimated to reduce the thoracic volume by 500 ml. This estimation, however, assumed that the diaphragm moves with a piston-like action and also makes assumptions about the shape of the rib cage and diaphragm. These authors suggested that induction of anaesthesia with halothane was associated with a 300-ml decrease in central blood volume [56]. However, Krayer and colleagues used three-dimensional dynamic spatial reconstruction in supine volunteers and found that cephalad displacement of the diaphragm did not contribute significantly to the reduction in FRC (fig. 4). They concluded that during thiopentone–fentanyl anaesthesia there was a significant increase in central blood volume [74].

Anaesthesia with ketamine is not associated with a reduction in FRC, and ventilation and perfusion are well matched [135]; children anaesthetized with ketamine tend to have an increased FRC, possibly as a result of laryngeal activity during expiration [118–120, 135].

In infants and young children, the outward recoil of the chest wall is less than in adults (see below), allowing the lungs to recoil closer to residual volume, and probably making any further reduction in lung volume during anaesthesia more significant in relation to gas exchange. The effect of anaesthesia on diaphragmatic movement and intrathoracic blood volume in infants and children requires further study.

Using computed tomographic scanning techniques in adults, one group of workers have shown that pulmonary densities develop in areas of collapse in the dependent regions of the lung. These may have adverse effects on gas exchange during and after general anaesthesia [16, 57, 129, 130, 134]. In 29 anaesthetized children aged 4 months to 7 yr, deaeration changes were demonstrated in the dependent areas of the lung in 81% of lung scans. There was no evidence of such changes in any of the scans from 52 sedated children of similar age [30]. As indicated earlier, *V*T may be as small as 4 ml kg^{-1} during anaesthesia with spontaneous breathing in infants and young children, so that respiration may take place low down on the pressure–volume curve [41, 104, 150]. This may exaggerate any effect of airway closure on gas exchange, as airways may remain closed for a greater percentage of *V*T.

In healthy, non-anaesthetized infants, lung volume is frequently maintained greater than true passive FRC by mechanisms which have seldom been studied during inhalation anaesthesia. Persistent EMG activity of intercostals and diaphragm has been demonstrated during inspiration [87]. The act of breathing, however, involves not only these muscles, but also the less well studied group of upper airway muscles, the function of which is to maintain a low resistance pathway in the upper airway and possibly regulate expiratory air flow by a varying degree of expiratory braking or throttling [8, 94]. In the newborn, afferent information has been shown to play an important part in the regulation and activation of these muscles, and in the co-ordination of their function, and active control of expiratory flow may play a key role in the ventilatory adaptation to birth [39]. Active laryngeal narrowing, which reduces expiratory air flow, is present in many infants up to at least 1 year of age [25, 94].

Summary. FRC is reduced significantly in recumbent subjects during general anaesthesia, with or without neuromuscular block, in adults and children. This reduction, which may affect gas exchange, is associated with changes in chest wall recoil, laryngeal

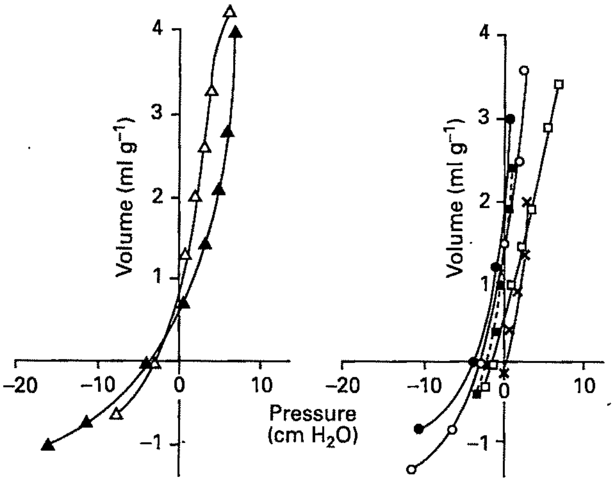

FIG. 5. Pressure–volume characteristics of thorax in paralysed 63-day-old (△) and adult (▲) goats (left) and paralysed younger goats (right) (■, □ = 3-day-old; × = 6-day-old; ●, ○ = 16-day-old). In younger animals, note very high compliance of the thorax above the mid position (horizontal axis). (From Avery and Cook [2].)

braking and intrathoracic blood volume but, at least in supine adults, little cephalad movement of the diaphragm. The magnitude of these changes needs further evaluation in infants and young children.

Pressure–volume relationships

The pressure required to inflate the respiratory system must overcome the recoil forces of lung and chest wall, which are arranged in series. As can be seen from figure 1, the pressure–volume curves of the lung, chest wall and total ventilatory system are different, both in slope and position. A shift of the pressure–volume curve of the lung to the right implies that a greater transpulmonary pressure is required to maintain a given lung volume, whilst a reduction in slope indicates an increase in elastance or "stiffness", that is, a reduction in compliance.

Measurements of the pressure–volume curve should be made under fairly static conditions, such as during a short period of breath-holding or temporary airway occlusion, to exclude pressure changes related to the flow-resistive properties of the ventilatory system. Difficulties in ensuring relaxation in the awake or sedated states may affect interpretation of the effects of anaesthesia and, as pressure–volume curves are not linear, comparisons of compliance before and after induction of anaesthesia must be made at the same lung volume. As intercostal and diaphragmatic activities are inhibited and vagal activity is reduced during active sleep, changes in the mechanics of the chest wall may occur also [14, 36, 98]. It is important, therefore, to record the sleep state when results obtained in infants and children under anaesthesia are compared with those obtained during sleep in the non-anaesthetized subject. Unfortunately, many of the published data, particularly in children, have been made either under dynamic conditions or at unknown lung volume, so that their interpretation is difficult.

Within the normal breathing range, the slope of the pressure–volume curve of the chest wall (abdominal wall, diaphragm and thoracic wall) is steeper in young than adult subjects [2] (fig. 5). Because the compliance of the chest wall (*C*w) is so large in young subjects, total respiratory compliance (*C*rs) reflects primarily the lung compliance (*C*L). For this reason, many of the studies carried out in infants have used the simpler measurement of *C*rs, which may be measured relatively easily by relating volume change to total pressure change across the ventilatory system after temporary airway occlusion. *C*L and *C*w require a knowledge of pleural pressure, which conventionally has been estimated from measurements of oesophageal pressure, known to be misleading in sick and pre-term infants [10, 55]. Moreover, both *C*rs and *C*w are affected by the degree of relaxation of the thoracic muscles, whilst *C*L is not. A stable pressure plateau maintained for at least 0.2 s during airway occlusion has been shown to indicate satisfactory relaxation and to give reproducible results [127]. The recoil pressure of the chest wall of young subjects is less than that of adult subjects, resulting in a less subatmospheric pleural pressure and rendering the lungs more prone to the development of atelectasis and collapse [11, 33, 48, 61, 109, 116].

Induction of anaesthesia in adults appears to be associated with a flattening of the slope and a shift to the right of the pressure–volume curve of the lung (fig. 6). Lung compliance does not appear to be reduced further by muscle paralysis [144]. In infants

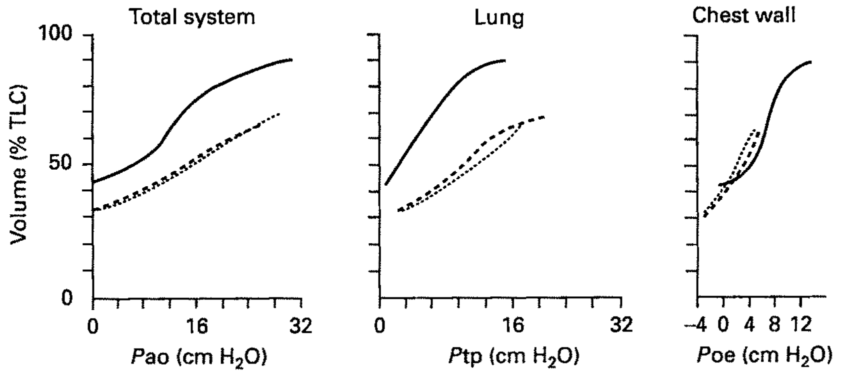

FIG. 6. Mean deflation pressure–volume relationships for total ventilatory system, lung and chest wall obtained from five supine subjects. Volume expressed as percent of control total lung capacity. *P*ao = Airway opening pressure; *P*tp = transpulmonary pressure; *P*oe = oesophageal pressure. — = Awake; ---- = anaesthetized; ... = anaesthetized–paralysed. (From Westbrook and colleagues [144].)

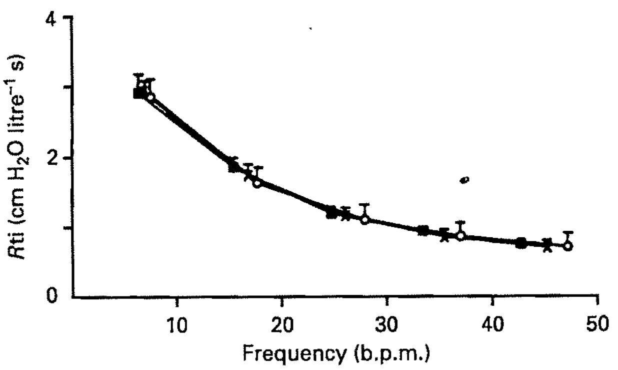

FIG. 7. Frequency-dependence of tissue resistance (*R*ti) in six isolated dog lungs (mean, SEM). Tidal volume/vital capacity = 0.1 (○), 0.2 (×) or 0.4 (■). (From Brusasco and colleagues [17].)

and young children, *C*rs is reduced during anaesthesia by almost 40% compared with the values found during sedation with triclofos and, as in the adult, neuromuscular block and controlled ventilation of the lungs *per se* do not appear to cause further reduction in compliance. *C*rs has been shown however, to be tidal volume-dependent in anaesthetized, paralysed infants and young children, in whom values approximating those in the non-anaesthetized, sedated state may be achieved by ventilating with tidal volumes similar to those measured during sedation [41, 42]. Controlling ventilation in this manner overcomes the regulatory changes which may influence *C*rs during spontaneous breathing, and improves lung volume. However, it may of itself cause a reduction in surfactant activity and does not, at least in adults, completely reverse either the atelectasis or the abnormalities in blood-gas tensions [57]. The magnitude of the changes in lung volume and compliance during anaesthesia in children appear to be position-dependent [60, 76], changes being greater in the lateral compared with the supine position.

Several mechanisms may be responsible for the reduction in lung compliance seen during anaesthesia. These include atelectasis, altered distribution of inspired gas and loss of surfactant. Disturbances in secretion and distribution of surfactant have been reported in animals and man after exposure of the lungs to increased airway pressure or inhaled volatile agents [5, 114], although recovery tends to be rapid on removal of the insult. Lung compliance remains unchanged during ketamine anaesthesia [120].

Summary. Induction of anaesthesia is associated with a change in the slope and position of the pressure–volume curve of the lung in adults and children. Possible mechanisms include loss of surfactant, atelectasis and altered distribution of inspired gas.

Pressure–flow relationships

Resistance to gas flow occurs when the gas within the lungs is in motion. Resistance to gas flow in the respiratory system (*R*rs) has both pulmonary (*R*L) and chest wall (*R*w) components. *R*L may be subdivided further into airways resistance (*R*aw) and pulmonary tissue resistance (*R*ti). *R*ti, an index of the pressure–volume hysteresis of the lung, has been shown in dogs to be the predominant component of *R*L at tidal volumes and ventilatory frequencies found during quiet breathing. There is some evidence to suggest that it is also a significant component of *R*L at physiological tidal volumes and frequencies in man [4, 29]. Both halothane and enflurane have been shown to reduce *R*rs in adults [78]. Halothane reduces both *R*aw and *R*ti in dogs, but does not change the relative contribution of *R*ti to *R*L [139, 140]. The relative contribution of *R*ti to *R*L does, however, decrease with increasing ventilatory frequency (fig. 7) [17] and may thus be less important in infants and young children than in adults, because of the increased frequencies seen during respiratory failure. Analysis of pressure–flow curves in infancy suggests the *R*ti may make only a minimal contribution to *R*L in infants [128].

Poiseuille's law states that, for laminar flow:

$$\text{Resistance} = \frac{8l\eta}{\pi r^4}$$

where l = length, r = radius and η = viscosity of the gas.

It is clear that changes in airway calibre have a marked effect on resistance, which varies inversely with the fourth power of the radius. This is likely to be of particular importance in infants, with their small airways. The rapid growth and increase in airway calibre occurring during early childhood leads to a correspondingly rapid reduction in airway resistance [96]. Thus small changes in airway calibre become less critical with increasing age [125].

Airway resistance may be altered by extrinsic or intrinsic factors [64]. The reduction in lung volume which occurs during anaesthesia leads to a secondary reduction in lung recoil, and this in turn leads to a loss of airway distending pressure. Peripheral airways with their large total cross-sectional area contribute relatively little to the total airway resistance, so that it is probably only changes in diameter of the central airways that are clinically significant [132]. Intrinsic factors which may alter airway resistance include alterations in tone of airway smooth muscle, intramural oedema, secretions in the airway lumen and the presence of a tracheal tube.

Contraction and relaxation of airway smooth muscle is regulated by neurotransmitters which bind to specific receptors on the cell surface. Intracellular transmission involves a group of G-proteins which link the surface receptors to their effectors. Intrinsic airway tone is modulated by a complex combination of humoral and neural factors involving the sympathetic, parasympathetic and non-cholinergic–non-adrenergic nervous systems. The currently used inhalation anaesthetics, halothane, enflurane and isoflurane, affect airway calibre in several ways, including a direct relaxant effect on airway smooth muscle, blocking of airway reflexes, inhibiting release of broncho-active inflammatory mediators and augmenting beta adrenergic tone. The relative importance of the various mechanisms is, however, still uncertain [64]. All three agents effectively antagonize the irritant effects of tracheal intubation on airway smooth muscle. In dogs, enflurane and isoflurane have been shown to attenuate the increase in pulmonary resistance induced by vagus nerve stimulation, whilst atracurium and pancuronium enhance it; vecuronium appears to have no significant effect. Although bronchoconstriction caused by neuromuscular blocking agents has conventionally been attributed to histamine release, recent work has suggested that it may in part be caused by antagonism of the M_2 receptors which are located presynaptically on postganglionic parasympathetic nerves, and which inhibit the release of acetylcholine. Gallamine is a known M_2 antagonist, and this property may be shared by pancuronium and atracurium [138].

The bronchodilator effects of ketamine are probably in part mediated sympathetically, but may also involve the parasympathetic nervous system and a direct effect on the airway smooth muscle.

There are few data on the effects of inhalation or i.v. anaesthesia on pressure–flow relationships in infants and young children, as a result in part of technical difficulties in studying patients in this age group. In infants, the measurement of *R*aw by whole body plethysmography is technically complicated [9] and the measurement of *R*L by oesophageal manometry is potentially unreliable [55]. The more recently described single breath measurements of *R*rs [95] are simpler to perform, but erroneous results are obtained in the presence of leaks or active expiratory effort. Using this technique, Shulman, Bar-Yishay and Godfrey found total resistance to be increased during ketamine anaesthesia in infants without a tracheal tube, although ketamine is a known bronchodilator [120]. The prolonged expiratory time constant seen in these children was thought to be caused by active laryngeal narrowing during expiration, rather than a change in the lower airways. Thiopentone has been shown to cause bronchoconstriction in clinical doses and bronchodilatation at slightly greater doses [79]. Tracheal irritation during intubation without neuromuscular block can be a potent cause of bronchospasm in children if the depth of anaesthesia is inadequate. The actions of anaesthetic agents and neuromuscular blocking drugs on airway smooth muscle in children have yet to be evaluated.

Summary. Tissue resistance is probably more significant in adults than has previously been thought, but its importance in infants and young children may be lessened because of their greater ventilatory frequencies. Changes in airway resistance, which are important when airways are small, may be brought about by changes in smooth muscle tone or changes within the lumen, such as the accumulation of secretions and oedema, and reduction in lung volume. The effect of anaesthetic agents and related drugs on airway smooth muscle tone in children has received little attention.

PATHOPHYSIOLOGY OF INTERMITTENT POSITIVE PRESSURE VENTILATION

Gas exchange

It has been well known for many years that general anaesthesia in adults with spontaneous breathing or intermittent positive pressure ventilation of the lungs (IPPV) causes some impairment of gas exchange [103, 131]. This results partly from the reduction in FRC which occurs on induction of anaesthesia with shunting of blood through unventilated areas of lung, and partly from alterations in the ventilation: perfusion ratio. Studies have suggested that the magnitude of the shunt and alveolar–arterial oxygen tension difference might correlate with the extent of densities seen with computed tomography [49, 57, 129, 130, 134]. Conflicting results have been reported in relation to the effect of positive end-expiratory pressure (PEEP) on the size of the densities and the magnitude of the shunt [16, 134]. These may reflect the limitations of the technology, as the imaged slices are not obtained simultaneously and assumptions must be made about the opacity of tissues lying between the imaged slices [111].

Differences exist between children and adults in relation to the distribution of ventilation and pulmonary perfusion. In the spontaneously breathing adult, ventilation and perfusion are distributed preferentially to the dependent parts of the lungs [6, 45, 47, 93, 143], with diversion of ventilation preferentially to the non-dependent parts during IPPV [112]. In spontaneously breathing children, however, the distribution of ventilation is similar to that seen during IPPV in adults [54]. This finding is of particular importance in children with unilateral lung disease, in whom oxygenation improves when the good lung is uppermost—the reverse of the situation in adults [32]. These findings suggest that there might be more ventilation–perfusion mismatch during spontaneous breathing in children, with less change occurring when IPPV is used. Change of posture from supine to lateral caused a greater decrease in ventilation:perfusion ratio in the dependent lung in children than in adults [12]. There seems to be little evidence of any difference in oxygen saturation between spontaneous ventilation and IPPV in children, presumably because oxygen enriched mixtures are invariably used during anaesthesia. The effect of IPPV on alveolar–arterial oxygen tension difference in children has not been studied widely.

The rapid ventilatory frequencies seen during spontaneous breathing in infants result in an increase in deadspace volume per minute [66]. Deadspace: tidal volume ratio increases with IPPV. Fletcher demonstrated a 19% increase in deadspace when children were turned to the lateral position for thoracotomy, with a reduction in deadspace and oxygen tension when the pleura was opened [43]. Gas exchange could be maintained only by increasing airway pressure, and both compliance and conductance were reduced after operation compared with preoperative values.

Pulmonary barotrauma

Long-term ventilation of the lungs in infants may cause serious barotrauma, particularly in the presence of respiratory distress syndrome of the newborn (RDS) [102], and Stocks has shown that airway resistance is increased throughout the first 1 yr of life after IPPV in this condition [126]. Although there is little evidence in humans to suggest that the short-term exposure to IPPV occurring during anaesthesia causes barotrauma, animal research has demonstrated the possibility of such adverse effects, particularly if the lungs are already damaged. An understanding of the physiological principles involved in mechanical ventilation of the lungs is important for optimum patient care [65]. Large inspiratory pressures and large tidal volumes have been shown to cause increased microvascular permeability and pulmonary oedema, retention of lung water and a decrease in the albumin: globulin ratio of pulmonary lymph [15, 18, 27, 108]. Recent improvements in ventilator design allow tidal volumes to be delivered at minimal peak inflation pressures [52] which have been associated previously with improved survival rates in infants with RDS [115]. Greater PEEP does not appear to produce such water retention and may even prevent surfactant depletion [27, 141], although the reason for these differences in the effect of pressure is not clear. High frequency ventilation was introduced in the hope that it would provide better gas exchange than conventional IPPV and reduce the risk of barotrauma because of the smaller peak airway pressures required. Despite initially encouraging results in animals [50], clinical results have been disappointing [117].

Little experimental work has been carried out on the effects of drugs on the musculature of the developing airway, although our understanding of the neural control of the airways is improving rapidly [7]. In neonatal lambs, pancuronium attenuates acetylcholine-induced muscle constriction, possibly by an effect on M_2 receptors as described above, and this may influence the susceptibility of the neonate to airway deformation during IPPV [148]. It has been claimed that neuromuscular block produced with pancuronium speeds recovery of the lungs in RDS, although this has been attributed to a reduction in airway pressure rather than any pharmacological effect of the blocking drug itself [110].

Postoperative ventilatory function

The impairment of gas exchange occurring during anaesthesia persists into the postoperative period [28, 70]. As children are potentially more susceptible to airway closure than adults, postoperative hypoxaemia might be expected to occur at least as frequently, if not more so. The densities seen on computed tomography scans in the dependent parts of the lung during anaesthesia persist well into the postoperative period, and may contribute to the significant decrease in mean oxygen saturation found after operation compared with preoperative values in ASA class I infants and children [97, 130]. Routine postoperative oxygen saturation monitoring would seem desirable, at least in the immediate recovery period.

Steward pointed out that pre-term infants are more prone to complications after anaesthesia, particularly life-threatening apnoeic episodes, than are full-term infants [124]. This may in part be caused by the fact that chest wall stability increases with gestational age [31]. Lui and colleagues suggested that anaesthesia may unmask a defect in ventilatory control in prematurely born infants younger than 41–46 weeks postconceptual age (PCA) and found that infants with a pre-anaesthetic history of idiopathic apnoea were particularly at risk after operation [86]. They suggested that such infants should not undergo surgical procedures as out-patients. Continuous postoperative monitoring is recommended for 12–48 h in pre-term infants younger than 60 weeks PCA, and non-essential surgery should probably be delayed until 44 weeks PCA [86, 124]. Caffeine has been shown to reduce the severity of postanaesthetic apnoea in ex-premature infants, but not to abolish it completely [142].

CONCLUSION

Marked age-related differences exist in respiratory physiology which make infants and young children more susceptible to the adverse effects of anaesthesia than adults. When spontaneous breathing is maintained, these effects can often be minimized by using light planes of anaesthesia supplemented by appropriate regional nerve block.

The effects of anaesthesia and IPPV on alveolar–arterial oxygen tension differences do not appear to be clinically significant when oxygen enriched mixtures are used, but may contribute to postoperative hypoxaemia. Further work is required on the effect of anaesthesia on chest wall recoil, laryngeal braking mechanisms and shifts in intrathoracic blood volume in children, and on the reasons for the change in slope of the pressure–volume curve. Tissue resistance is less significant at rapid ventilatory frequencies, but changes in airway resistance may be more important in small subjects. The role of the M_2 receptor in control of muscle tone requires evaluation, as do the reasons for postoperative disturbances in the control of breathing, especially in premature and ex-premature infants.

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SHORT COMMUNICATIONS

EVALUATION OF A DISPOSABLE PATIENT-CONTROLLED ANALGESIA DEVICE IN CHILDREN

M. IRWIN, J. A. GILLESPIE AND N. S. MORTON

SUMMARY

A disposable patient-controlled analgesia (PCA) device was evaluated in 20 children after major abdominal, urological and orthopaedic surgery. All patients were given a high dependency level of nursing care in general wards. Efficacy (as assessed by hourly pain scores) was comparable to that achieved in a matched control group of 20 children who used the Graseby PCA system. Safety was confirmed by monitoring arterial oxygen saturation, sedation scores and ventilatory frequency. Morphine consumption was similar with the two techniques, but varied widely between patients. The disposable device has a complementary role to play in the provision of a comprehensive pain relief service for children.

KEY WORDS

Anaesthesia: paediatric. Equipment: patient controlled analgesia system. Pain: postoperative.

Pain management techniques in paediatric patients have been reviewed comprehensively recently [1]. Patient-controlled analgesia (PCA) may be used safely in suitably selected children of a minimum of 5 years of age [2]. PCA is an important technique [3] and suitable dosage regimens and monitoring procedures have been developed for children [4]. The present study was undertaken to compare the clinical performance of the disposable PCA infusor (Baxter Healthcare Ltd, Thorpe Lea Manor, Thorpe Lea Road, Egham, Surrey TW20 8HY) [5,6] with an electronic PCA system (Graseby Medical Ltd, Colonial Way, Watford, Herts WD2 4LG) in children after major surgery.

METHODS AND RESULTS

We studied 40 children aged 4–17 yr undergoing major abdominal, urological or orthopaedic surgery. PCA devices were used after operation as part of a large study of various PCA techniques for which hospital Ethics Committee approval had been granted. Parental consent was obtained for the use of PCA and all children were visited beforehand to have the technique explained and to practise with demonstration models. An assessment was made of the child's ability to understand and use the devices. Twenty children used the disposable PCA infusor (fig. 1). The elastomeric reservoir of the infusor was filled with morphine sulphate 2 mg kg^{-1} in 0.9% saline 50 ml. The infusor (2C1073) empties at a constant rate of 5 ml h^{-1} into a wristwatch-style patient control module which incorporates a reservoir with a volume of 0.5 ml. Flow occurs into the reservoir until it is full and then ceases. No flow can go to the patient as the outlet from the reservoir is occluded by a spring-loaded pinch mechanism. When the button on the wristwatch is pressed, this occlusion is released and a bolus dose of morphine 20 μg kg^{-1} is delivered into the i.v. cannula via a one-way valve. The reservoir in the watch is refilled in 6 min, providing a nominal lockout interval of 6 min (this is not a true lockout interval, because button presses within this 6-min period cause any contents which have accumulated in the wristwatch reservoir to be delivered). No background infusion was used. The monitoring regimen developed by our department [4] was used to assess efficacy (hourly pain scores), adverse effects (hourly sedation scores, continuous arterial oxygen saturation while breathing room air recorded hourly, hourly ventilatory frequency, occurrence of nausea, vomiting and venous sequelae) and morphine consumption (residual volume of reservoir recorded hourly). With this procedure, excessive sedation is defined as a sedation score of 4 (unrousable) and significant respiratory depression is defined as a ventilatory frequency of 12 b.p.m. associated with desaturation to 90% in a child aged 5 yr or more. All children were managed in the general ward situation with a high dependency level of nursing care (one nurse per two patients). Each child who used the disposable device was paired with a child of the same age and weight undergoing the same operation who used the Graseby electronic PCA system programmed to deliver morphine 20 μg kg^{-1} with a lockout interval of 5 min and no background infusion (our current PCA regimen). These children were assessed and managed in the same way. All children in the study had an appropriate regional block for intraoperative and early postoperative pain relief.

The results (table I) show that equally good analgesia was achieved with both systems as demonstrated by the low hourly mean pain scores. This is supported further by the fact that only 34 individual

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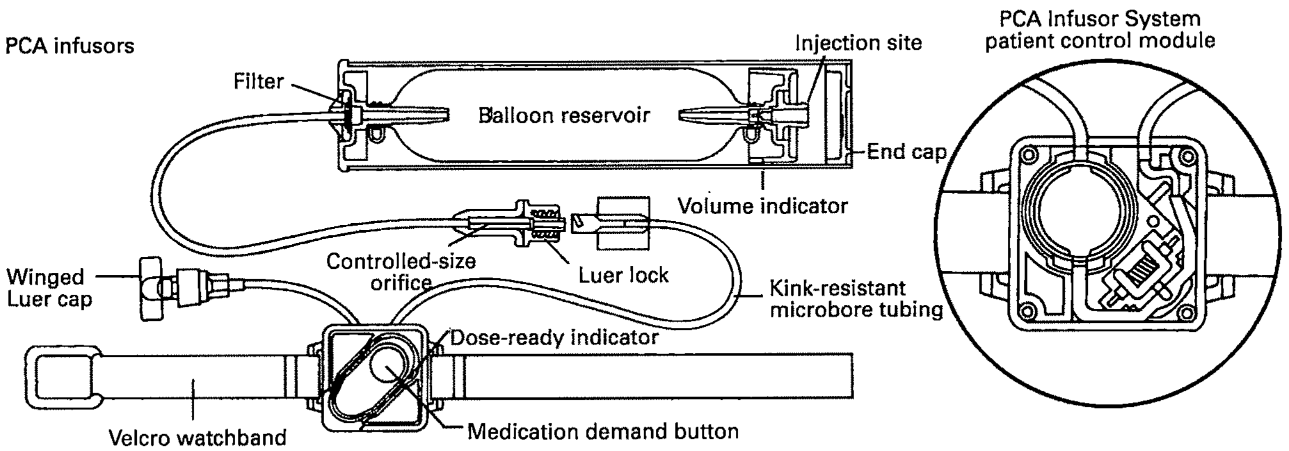

FIG. 1. Diagrammatic representation of the device. The disposable PCA device consists of an elastomeric balloon filled with morphine which empties into a wristwatch reservoir. When the button on the wristwatch is pressed, a bolus of opioid is delivered into the i.v. cannula via a Cardiff one-way valve (Vygon U.K. Ltd). The wristwatch should be attached loosely, to prevent occlusion of the i.v. cannula and the pulse oximeter probe on the thumb. It is important also to leave the patient's other (preferably dominant) hand free to activate the device.

TABLE I. *Comparison between performance of the disposable PCA infusor and that of the Graseby PCAS in children after major surgery (mean (range))*

	Disposable infusor ($n = 20$)	Graseby PCAS ($n = 20$)
Age (yr)	9.91(4–17)	9.74(5–17)
Sex (M:F)	13:7	10:10
Weight (kg)	31.9 (17–62)	30.4 (20–54)
Time on PCA (h)	49(10–96)	52.25(26–91)
Ventilatory frequency (b.p.m.)	20.52(10–40)	20.64(10–32)
Mean minimum (b.p.m.)	16.1	16.7
Time (%) at		
Sp_{O_2} 95–100%	85	88.5
Sp_{O_2} < 90%	0	0.35
Least S_{pO_2} (%)	90	87
Sedation score	0.65(0–3)	0.74(0–3)
Pain score	0.67(0–3)	0.82(0–3)
Mean consumption of morphine		
(μg kg^{-1} h^{-1})	20.30(8.9–43.1)	21.98(8.4–36.2)
(mg kg^{-1} day^{-1})	0.49(0.21–1.035)	0.53(0.20–0.87)

scores of 2025 recorded were rated as "very sore" (19 in the Graseby group, 15 in the disposable infusor group). No instances of oversedation or significant respiratory depression occurred. Sp_{O_2} values were nearly all in the range 95–100%. The nadir of Sp_{O_2} was 87% in the group using the disposable device and 90% in the group using the electronic system. These desaturations were transient and were not associated with slow ventilatory frequencies or oversedation. The incidence of nausea and vomiting was comparable in each group. Mean morphine consumption was similar in the two groups with a 4- to 5-fold range of utilization.

COMMENT

The clinical performance of the disposable PCA infusor was satisfactory in our children, providing as good analgesia as the electronic PCA device. Adverse effects were minimal and comparable in severity.

Most children were managed satisfactorily with the PCA settings used in this study. Previously, we used a longer lockout interval of 10 min [4]. Experience gained in a subsequent 50 children undergoing major surgery has led us to conclude that a shorter lockout interval allows the child to achieve an acceptable level of analgesia more rapidly. The disposable infusor is inherently less flexible than electronic devices, in that dosage and lockout interval are fixed when the device is filled. Morphine requirements varied widely between patients and at different times in an individual patient's postoperative course. PCA settings may therefore have to be adjusted to achieve optimum analgesia while minimizing adverse effects. No children in this study, however, required adjustment of bolus dose size or lockout interval.

We did not use a background infusion in this study, but another version of the device is available which allows a background infusion by incorporating two Y-pieces in the circuit such that one limb bypasses the wristwatch reservoir.

An incorrect concentration of drug may be used when filling either system. The only other "programming error" with the disposable device would be to use the wrong infusor, as three models are available which empty at different rates (0.5, 2 and 5 ml h^{-1}). The pattern of demands cannot be charted for the disposable device, but morphine consumption may be measured by recording the rate of emptying of the reservoir. Small children may have difficulty in activating the devices, particularly when drowsy or when visual accommodation is affected by opioids. We found that some children were more able to locate and operate the wristwatch button of the disposable device when it was worn on the palmar aspect of the wrist. Most children using PCA devices for postoperative analgesia need initial reminders and encouragement to recognize when and how to activate the system and this applies equally to electronic and disposable systems.

We conclude that suitably selected children aged at least 5 yr may use PCA safely if a high dependency level of nursing care and a monitoring regimen are used to assess efficacy and adverse effects. The disposable device is an alternative to electronic systems and may have advantages in terms of cost; there is less capital outlay, no maintenance cost and less wastage cost when the device is not in use.

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STABILITY OF FENTANYL, BUPIVACAINE AND ADRENALINE SOLUTIONS FOR EXTRADURAL INFUSION

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SUMMARY

Fentanyl and bupivacaine were tested for their stability when diluted with 0.9% sodium chloride to 4 μg ml^{-1} and 0.1%, respectively, in 100-ml polyvinyl chloride (PVC) bags, alone and in combination, with and without adrenaline 1:200000. Changes in drug concentration and pH were investigated for 56 days. The combination of fentanyl, bupivacaine and adrenaline was tested under varying environmental conditions of 35 °C, 4 °C, −18 °C, room temperature, darkness and after autoclaving. Fentanyl and bupivacaine were adsorbed onto PVC, resulting in reductions of 12.6% and 9.6% drug mass, respectively, at day 3, but remained stable thereafter. Adrenaline was progressively degraded to a maximum reduction of 37.3% at 35 °C by day 56. Solutions containing adrenaline became more acidic over 56 days. Fentanyl and bupivacaine were stable.

KEY WORDS

Analgesics: fentanyl. Anaesthetics, local: bupivacaine with adrenaline. Anaesthetic techniques: extradural infusion, in vitro *stability.*

Combination extradural opioid and local anaesthetic solutions are used in clinical practice with little information on their chemical stability [1]. Drug incompatibility, adsorption onto containers, photodegradation, precipitation with pH alteration and temperature and storage decay may have clinical implications [2]. Increasing extradural infusion rates with time to maintain analgesia have been ascribed to tachyphylaxis, without consideration of drug decay [3]. Adrenaline, reported to reduce extradural fentanyl requirement and complications [4], oxidizes with light and high temperatures which, if significant in solution, may make conclusions drawn from studies using the drug doubtful. Drug decay may result in degradation products which may potentially be neurotoxic or pharmacologically active. Microprecipitates may promote granulation tissue formation or create a nidus for extradural infection.

This study investigated the concentration and pH stability of fentanyl, bupivacaine and adrenaline in combinations used in the normal clinical range.

METHOD AND RESULTS

Seventy-eight 100-ml bags of 0.9% saline (Delta West batch No. 56791) were allocated to 13 groups of six bags. Drug combination groups were fentanyl 4 μg ml^{-1} alone (F), 0.1% bupivacaine alone (B), fentanyl 4 μg ml^{-1} and 0.1% bupivacaine (FB) and fentanyl 4 μg ml^{-1}, adrenaline 1:200000 and 0.1% bupivacaine (FAB).

Each bag was prepared by removing a corresponding volume of saline and adding the required drugs via Terumo PVC syringes and 23-gauge disposable needles through the rubber injection port. Eight millilitre of fentanyl citrate 50 μg ml^{-1} (David Bull, batch 0012540) was added to achieve a concentration of 4 μg ml^{-1}, 0.5% bupivacaine 20 ml plain (Marcain, Astra, batch 1976/2) was added to achieve a 0.1% bupivacaine solution and adrenaline acid tartrate 1:1000 0.5 ml (Astra, batch 9960) was added to achieve a concentration of adrenaline 1:200000. The order of injection of the drugs was always smallest to largest volume.

Each bag was mixed for 1 min and control (day 0) samples (0.5–1 ml) taken via the rubber injection port using a fresh syringe and 25-gauge needle for drug assay and pH measurement. The bags were placed into their allotted environment. The F, B, FB and an FAB group were kept on the laboratory bench at room temperature and lighting (no direct sunlight) for 56 days. For testing under varying environmental conditions, a further four FAB groups were placed in a black bag and stored in a dark cupboard (dark), kept in a refrigerator at 4 °C (cold), kept in a waterbath at 35 °C in darkness (hot) or placed in a freezer for 28 days at −18 °C (frozen). The bags of the frozen group were left undisturbed in the freezer until day 28, when they were thawed in darkness, sampled, autoclaved immediately at 121 °C for 30 min and sampled again. All other bags were sampled at 1, 2, 3, 7, 14, 21, 28 and 56 days.

A 200-μl aliquot of each sample from the FAB group was passed through a Millex 0.45 μm filter (Millipore) before being assayed to remove microprecipitates which may have formed in the bags

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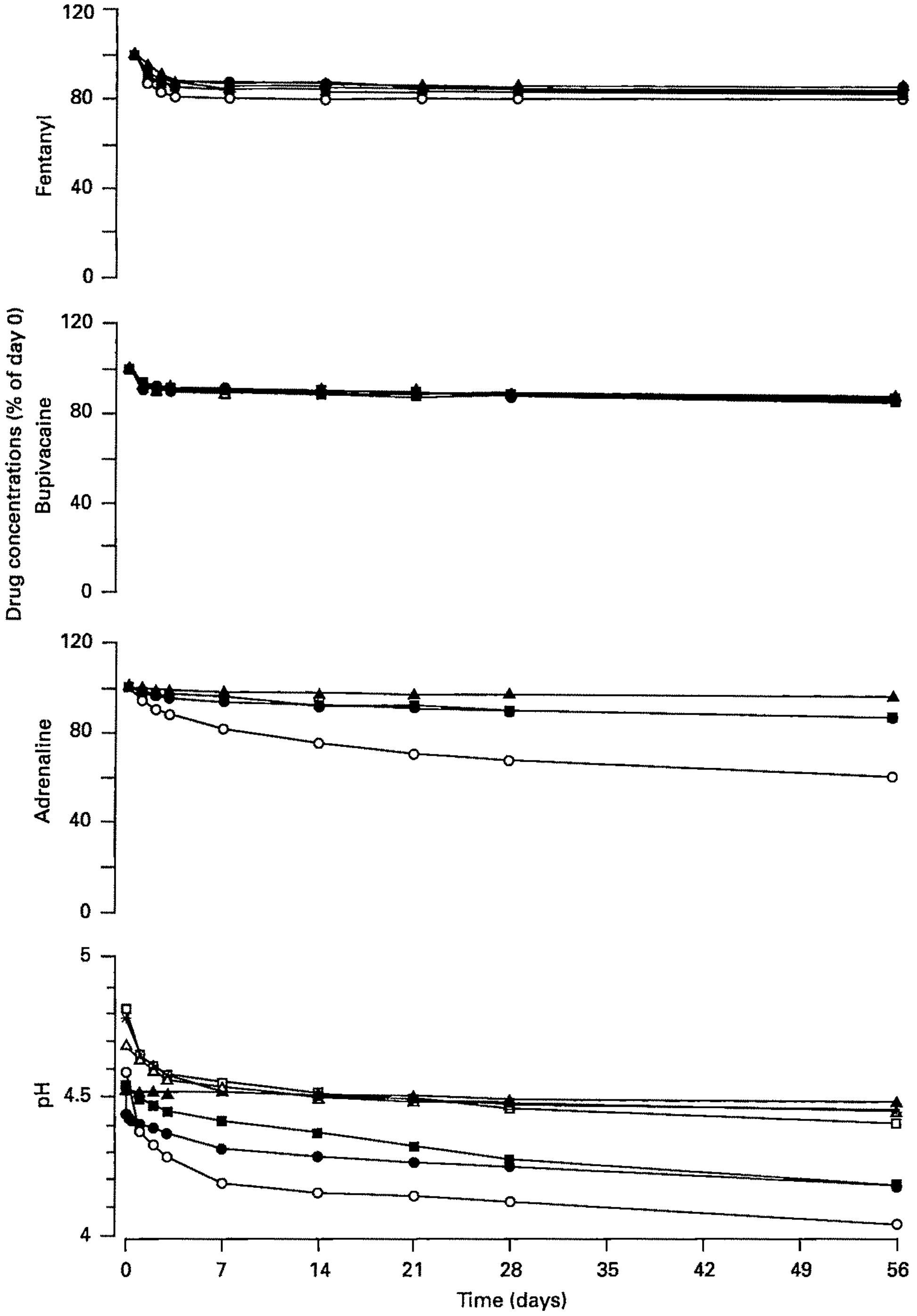

FIG. 1. Mean fentanyl, bupivacaine and adrenaline concentrations and pH in each group from day 0 to day 56. ● = Fentanyl+adrenaline+bupivacaine; ✱ = fentanyl+bupivacaine; △ = fentanyl; □ = bupivacaine; ■ = dark; ▲ = cold; ○ = hot.

during the study. Five groups of drug-free bags acted as controls for the effect of different environments on pH.

Fentanyl, bupivacaine and adrenaline concentrations were measured by high pressure liquid chromatography (HPLC). Quantitation was by peak height ratio to external standards on each analysis day. Fentanyl concentrations were measured by direct injection of 20 µl of infusion bag solution onto a 15 cm × 3.9 mm Waters uBondapak CN column with a mobile phase of acetonitrile–dipotassium hydrogen phosphate 0.015 mol litre^{-1} (25:75) (pH 7.0). The within-day coefficient of variation was 1.83% at 4.0 mg litre^{-1} ($n = 6$) with detection at 210 nm. The bupivacaine assay consisted of direct injection of 5 µl of the infusion bag solution onto a 15 cm × 3.9 mm Waters uBondapak C_{18} column with a mobile phase of acetonitrile–potassium dihydrogen phosphate 0.05 mol litre^{-1} (30:70) (pH 3.2). The within-day coefficient of variation was 1.12% at 1.0 mg ml^{-1} ($n = 6$), also at 210 nm. For adrenaline, the method was direct injection of 50 µl of infusion bag solution onto a 15 cm × 3.9 mm Waters Novapak column using a mobile phase of acetonitrile–potassium dihydrogen phosphate 0.05 mol litre^{-1} (25:75), sodium dodecyl sulphate 0.005 mol litre^{-1} and disodium ethylenediamine tetra-acetic acid 0.001 mol litre^{-1} at pH 4.5. The within-day coefficient of variation was 2.41% at 5 mg litre^{-1} ($n = 6$) at 210 nm.

A Pye-Unicam Model 292 pH meter and Triton 124ABNC microelectrode calibrated with pH 4 and pH 7 standards on each day of analysis were used for all pH measurements.

Differences in concentration and pH between sets of time and environment data were determined with paired, one-tailed Student's *t* tests adjusted for multiple comparisons with the Bonferroni correction for each drug independently. The concentrations for each drug between day 3 and day 56 in each environment group were subjected to multivariate analysis of variance (MANOVA), with subsequent univariate analysis of variance (ANOVA) for each group. The filtered samples of bags of the FAB group were compared with their unfiltered counterparts using MANOVA. $P < 0.05$ was considered significant for all tests.

Fentanyl concentrations in bags of all groups decreased significantly over the first 3 days, with means ranging from 86.1% to 88.0% of control and thereafter a small but not significant decrease to day 56 (fig. 1). The concentration decline of 18.8% in the first 3 days in the hot group was significantly larger than the average 12.6% in the other environmental groups at day 3; this difference was not maintained at day 56. Freezing the bags had no effect on the change in concentration, which decreased to 87.4% of the initial value at day 28, with autoclaving producing a further small reduction in concentration to 83.4%.

Bupivacaine concentration decreased significantly over the first 3 days by an average of 9.6% with a range of means of 90.7% to 92.1% of control and no differences between the groups (fig. 1). A further small decrease in concentration to day 56 was not significant. Freezing appeared to slow the concentration change with bupivacaine, declining 5.9% at day 28 in the frozen group compared with an average of 10% in the other groups at day 28. This just failed to reach significance ($P = 0.065$). Autoclaving was associated with a significant further decrease in concentration, to 83.8% of control.

Adrenaline behaved differently from the other drugs (fig. 1). Although all groups showed a decrease in adrenaline concentration of 1.4–5.0% by day 3, the only group to decrease significantly was the hot group, to 81.2% of control. After 56 days, adrenaline concentration exhibited a significant decrease of 11.1% in the FAB group. Adrenaline was particularly sensitive to temperature, with decreases of only 2.3% (not different from day 0) when kept at 4 °C (cold) and 37.3% when exposed to 35 °C (hot). Both groups were significantly different from the FAB group at room temperature at this time. The rate of adrenaline concentration change was not affected by light. Freezing the bags prevented a change in concentration, but autoclaving was associated with a decrease from 98.4% to 91.2%.

There was no evidence of precipitation of any of the drugs.

The pH decreased over 56 days from 4.54 to 4.20 in the FAB group. Groups lacking adrenaline showed a similar decay, starting from a significantly greater pH with means of 4.69 (F), 4.78 (B) and 4.82 (FB), which remained greater over the 56 days. The cold and dark groups had significantly greater pH values at day 3 (4.51 and 4.45, respectively), while in the hot group the decrease was to a smaller pH (4.29) than that (4.37) in the FAB group at this time. By day 56, the cold group pH was still not different from the day 0 value, that of the hot group was significantly smaller (4.07) and the dark group pH was no longer different from that of the FAB group (4.20). Freezing prevented the decrease in pH, but autoclaving produced a large decrease, from 4.51 to 3.80 (fig. 1).

The drug-free bags showed no significant differences from day 0 at either day 3 or day 56 or between groups. Neither freezing nor autoclaving was associated with any significant change.

COMMENT

Fentanyl and bupivacaine prepared in 0.9% saline PVC bags, alone or in combination, exhibited an early rapid reduction in concentration over the first 3 days, after which concentration was steady to day 56. The observed change in bupivacaine and fentanyl solutions kept at room temperature (9.6% and 12.6%, respectively) at day 3, although greater than the respective allowable shelf-life drug mass reductions of 7.5% [5] and 10% (Janssen Cilag), represent clinically insignificant reductions in delivered drug for extradural analgesia. Tachyphylaxis of extradural analgesic solutions cannot, therefore, be explained by diminishing solution concentration.

Early reductions in drug concentrations followed by a plateau phase are probably caused by saturable adsorption of drug onto the container surface. Weak bases such as fentanyl and bupivacaine are known to adsorb onto plastic. However, the greater reduction in fentanyl concentration compared with bupivacaine may be a reflection of the greater lipophilicity of fentanyl [6]. Individual drug decreases in concentration were not significantly different between the FAB, FB and F and B groups, indicating a lack of competition for adsorption sites. Other potential causes of reducing drug concentrations are precipitation and degradation. Precipitation was not detected by HPLC and the stability of drug concentration from day 3 to day 56 indicates an absence of significant degradation for both drugs.

Fentanyl adsorption to below shelf-life concentrations, while accelerated by heating to 35 °C, was not prevented by freezing, which raises difficulties for longer term storage in PVC. Newer plastics or glass may be required for commercial preparation and storage.

Degradation via oxidation is the likely cause of the heat sensitive progressive decrease in solution pH and adrenaline concentration in the FAB groups. Oxidation is consistent with our observation of increasing discolouration of FAB solutions as a result of formation of known acidic oxidation products, adrenochrome (pink) and melanin (brown). This has clinical implications. Reduced adrenaline concentration and pH of extradural solutions may allow greater drug washout of fentanyl and bupivacaine and decrease the non-ionized fraction of both drugs in the extradural space. It is therefore important for scientific publications to state the method of preparation, storage time and conditions of storage of adrenaline-containing solutions when making conclusions about adrenaline efficacy for extradural administration. Possible effects that adrenaline degradation products may have in the extradural space and the buffering capacity of the extradural space to acidic solutions are unknown.

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EFFECT OF DOXAPRAM ON NEOSTIGMINE EVOKED ANTAGONISM OF VECURONIUM NEUROMUSCULAR BLOCK

M. ORLOWSKI AND B. J. POLLARD

SUMMARY

We have examined the effect of doxapram on neostigmine-evoked antagonism of vecuronium neuromuscular block in a double-blind study in anaesthetized patients. Neuromuscular transmission was measured with a Datex Relaxograph. The mean time to recovery of the first contraction of the train-of-four (T1) from 25% to 75% was significantly longer in the presence of doxapram (138 (SEM 21) s; $n = 23$) than in its absence (95 (13) s; $n = 29$) ($P = 0.014$). The recovery of the train-of-four ratio was prolonged also in the presence of doxapram, although this difference was not statistically significant.

KEY WORDS

Analeptics: doxapram. Antagonists: neostigmine. Interactions. Neuromuscular relaxants: vecuronium.

Doxapram is a potent respiratory stimulant which has been used in clinical practice for many years. The mode of action of doxapram is thought to be related to an increase in the sensitivity of both central and peripheral chemoreceptors [1–3].

An effect of doxapram at the neuromuscular junction has been demonstrated previously *in vitro* [4]. Doxapram alone augments neuromuscular transmission, probably by a presynaptic action while, in the presence of a partial non-depolarizing neuromuscular block, transmission is inhibited; probably a post-junctional effect.

The time when doxapram is most likely to be used clinically is at the end of an anaesthetic, to stimulate ventilation and to enhance recovery, which is also when recovery from neuromuscular transmission is awaited. It is possible that the addition of doxapram to the dynamically changing situation within the neuromuscular junction at this time might introduce unwanted complications. This study was designed therefore to examine the effect, if any, of doxapram on the evoked antagonism of neuromuscular transmission.

METHODS AND RESULTS

Following Ethics Committee approval, we studied 52 healthy adult patients (ASA I or II) undergoing elective gynaecological surgery. All patients were premedicated with lorazepam 2–3 mg orally 90 min before operation. On arrival in the anaesthetic room, five self-adhesive surface electrodes were attached to the patient's right hand and i.v. cannula inserted into the left forearm. All drugs were administered into a fast running infusion connected to this cannula. The electrodes were arranged so as to record the compound EMG from the adductor pollicis muscle produced by stimulation of the ulnar nerve at the wrist using a Relaxograph (Datex).

Anaesthesia was induced with fentanyl 100 μg and sufficient thiopentone to abolish the eyelash reflex. The patient was allowed to breathe 70% nitrous oxide in oxygen with 0.5% halothane via a Magill circuit. Ventilation was assisted if necessary and normocapnia maintained. The calibration sequence of the Relaxograph was activated and a control recording obtained. Vecuronium was then administered in an initial dose of 0.08 mg kg^{-1}. Further increments of vecuronium were given, if required, to maintain the first response of the train-of-four (T1) less than 10% throughout surgery. Anaesthesia was maintained with 70% nitrous oxide with 0.5% halothane and further increments of fentanyl as required. At the conclusion of surgery, T1 was allowed to recover spontaneously to 20% of control, at which point the antagonists were administered.

Patients were allocated randomly to two groups in a double-blind manner. Patients in group 1 received neostigmine 0.05 mg kg^{-1} and glycopyrronium 0.01 mg kg^{-1} followed immediately by doxapram 0.5 mg kg^{-1}. Patients in group 2 received neostigmine 0.05 mg kg^{-1} and glycopyrronium 0.01 mg kg^{-1} followed by normal saline. The doxapram or saline was given from previously prepared randomly coded ampoules.

Train-of-four was monitored at 20-s intervals throughout surgery and changed to 12-s intervals before antagonism of neuromuscular block. When T1 had recovered to a maximum and the train-of-four ratio (T4:T1) (TR) to > 0.75, anaesthesia was discontinued and the trachea extubated when the patient was awake.

The time of recovery of T1 from 25% to 75% of control and of T4:T1 from 0.25 to 0.75 were measured. The groups were compared using the Mann–Whitney *U* test.

The two groups did not differ significantly in mean body weight, duration of operation or total dose of vecuronium (table I).

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TABLE I. *Mean* (SEM) *patient data, dose of vecuronium, duration of surgery and times of recovery from neuromuscular block with and without doxapram.* *P < 0.05 *compared with control*

	Group 1 (Doxapram)	Group 2 (Control)
n	23	29
Weight (kg)	62 (3.4)	60 (2.3)
Vecuronium total dose (mg)	7.0 (0.8)	6.0 (0.4)
Duration of surgery (min)	46 (6)	40 (4)
Recovery time (s)		
T1 25% to 75%	138 (21)*	95 (13)
T4:T1 0.25 to 0.75	252 (25)	221 (22)

The mean time for recovery from 25% to 75% was greater in the doxapram group (138 s) than in the control group (95 s) ($P = 0.014$). Recovery of T4:T1 from 0.25 to 0.75 was also greater in the doxapram group (252 s) compared with the control group (221 s), but this difference was not significant (table I).

COMMENT

This study suggests that the presence of doxapram retards neostigmine-induced antagonism of a vecuronium neuromuscular block. The antagonism of a neuromuscular block is complex and there are several possible ways in which doxapram could impede the process. A direct effect on the motor neurones to reduce their rate of firing seems unlikely. A previous *in vitro* study demonstrated no direct effect of doxapram on muscle in concentrations greater than would have been achieved in this study [4]. It would seem most likely, therefore, that the observed effect of doxapram is within the neuromuscular junction. This is reinforced by previous work which confirmed the existence of an inhibitory effect of doxapram on a partially blocked neuromuscular junction [4]. The study concluded that the action was taking place at the postjunctional receptor site, although the precise action at the receptor remains to be determined.

Vecuronium is 30% bound to plasma proteins [5]. It is possible that doxapram might displace vecuronium from extrajunctional binding sites, an action which would increase the unbound fraction of vecuronium. In view of the dependence of neuromuscular block on the free concentration of vecuronium at the neuromuscular junction, the extent of block would effectively increase, and this might be reflected as a delay in antagonism.

An interaction between doxapram and either neostigmine or cholinesterase has to be considered also. If doxapram were to inhibit the action of cholinesterase, or to reduce the ability of neostigmine to combine with or to inactivate cholinesterase, antagonism of neuromuscular block might be prolonged. No effect of doxapram was found on the activity of the cholinesterase from rat diaphragms *in vitro* [4]. However, a chemical interaction with neostigmine, or an effect on the interaction between neostigmine and cholinesterase cannot be excluded.

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MYOCARDIAL DEPRESSANT EFFECT OF NITROUS OXIDE AFTER CORONARY ARTERY BYPASS GRAFT SURGERY

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SUMMARY

We have studied the cardiovascular effects of nitrous oxide after cardiac ischaemia–reperfusion injury caused by aortic cross-clamping and unclamping during coronary artery bypass grafting (CABG). At the time of chest closure, 20 patients were allocated randomly to receive oxygen and air ($FI_{O_2} = 0.5$) or 50% nitrous oxide in oxygen in addition to anaesthesia with fentanyl. Nitrous oxide significantly decreased mean arterial pressure ($P < 0.01$) and cardiac index ($P < 0.05$), which suggests that nitrous oxide with fentanyl may significantly depress left ventricular performance after CABG. Although ischaemia–reperfusion cardiac injury did not appear to increase the myocardial depressant effect of nitrous oxide, the use of nitrous oxide is not recommended immediately after CABG.

KEY WORDS

Anaesthetics, gaseous: nitrous oxide. Heart: myocardial depression. Surgery: coronary artery bypass graft.

The addition of nitrous oxide to established anaesthesia has been reported to be associated with deleterious effects on myocardial function before coronary artery bypass graft surgery (CABG) [1]. These results are consistent with a study showing a depressant effect of nitrous oxide on myocardium supplied by stenotic coronary arteries [2]. However, the haemodynamic effects of nitrous oxide have not been well studied after myocardial reperfusion [1]. Aortic cross-clamping and unclamping during CABG expose the patient to unavoidable cardiac ischaemia–reperfusion injury with formation of free radicals [3] and nitrous oxide has been shown to enhance the production of hydroxyl radicals [4].

The purpose of the study was to determine if nitrous oxide altered cardiac function immediately after CABG.

METHODS AND RESULTS

After approval from the Committee for Ethics in Clinical Investigation of our Institution and informed consent from each patient, we studied 20 patients (two women, 18 men; ages 51–75 yr) undergoing CABG. Preoperative antianginal therapy was maintained until the day of surgery. Patients with preoperative cardiac failure (ejection fraction less than 40%), with a low cardiac output after cardiopulmonary bypass or requiring inotropic medication were excluded.

Anaesthesia was induced and maintained with fentanyl (0.006 mg kg^{-1} followed by 0.006 mg kg^{-1} h^{-1}), flunitrazepam 0.03 mg kg^{-1} and pancuronium 0.1 mg kg^{-1}. In all patients a 7-French gauge thermodilution pulmonary catheter and a radial artery catheter were inserted after induction of anaesthesia. Ventilation of the lungs was controlled using 50% oxygen (oxygen–air) except during cardiopulmonary bypass (CPB), when 100% oxygen was used. Cardiac arrest was induced by clamping the aorta, followed by infusion of a cardioplegic solution into the aortic root until myocardial temperature was 15 °C or less. General body temperature was reduced to 25–30 °C during cardiac arrest. To avoid air embolism in venous grafts, proximal anastomoses were performed first with partial clamping of the aorta during CPB; afterwards, distal coronary grafting was performed after cardioplegic arrest of the heart, and each venous graft was purged with either cardioplegic solution (300 ml) or, for the last distal coronary graft, by aortic unclamping. After CABG during skin closure, patients were allocated randomly to one of two groups: control group ($n = 10$) and nitrous oxide group (N_2O, $n = 10$). Control patients received oxygen and air ($FI_{O_2} = 0.5$) throughout the study. N_2O patients received 50% nitrous oxide in oxygen until equilibrium was achieved (Capnomac, Datex).

Systemic haemodynamic values were measured during stable ventilation with oxygen–air in both groups and after nitrous oxide had been administered for 5 min in the N_2O group or 5 min after the initial measurement in the control group. FI_{O_2} and end-tidal carbon dioxide concentration were unchanged during the study period. Each measurement period took about 10 min, and neither medication nor fluid was administered during the period of the study.

Two-way repeated measures ANOVA and Student's t test with Bonferroni's correction were used to assess differences between and within groups.

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TABLE I. *Haemodynamic data (mean (SD)). HR = Heart rate; MAP = mean arterial pressure; PCWP = pulmonary capillary wedge pressure; PAP = pulmonary artery pressure; CI = cardiac index; SVR = systemic vascular resistance; PVR = pulmonary vascular resistance. Significant differences*: *P < *0.05 compared with baseline*; †P < *0.05*; ††P < *0.01 between groups*

	Control group		N_2O group	
	O_2/Air	O_2/Air	O_2/Air	O_2/N_2O
HR (beat min^{-1})	83.7 (18.1)	83.7 (17.9)	81.6 (15.7)	76.6 (15.5)
MAP (mm Hg)	85.7 (7.3)	85.5 (9.7)	80.7 (9.1)	67.5 (15.2)*††
PCWP (mm Hg)	14.9 (5.5)	14.1 (4.9)	16.4 (4.7)	15.4 (4.2)
PAP (mm Hg)	7.3 (3.3)	7.8 (3.5)	7.5 (2.8)	7.0 (2.4)
CI (litre min^{-1} m^{-2})	2.49 (0.61)	2.41 (0.60)	2.37 (0.44)	1.92 (0.42)*†
SVR (dyn s cm^{-5})	1511 (355)	1566 (413)	1353 (282)	1399 (403)
PVR (dyn s cm^{-5})	169 (75)	189 (95)	149 (59)	190 (66)

A calculation of statistical power showed that the groups studied would have demonstrated a 13% change in MAP and a 15% change in CI with a power of 0.8.

The two groups did not differ in respect of patient characteristics or surgical procedure (aortic cross-clamping time, CPB time and number of coronary arteries bypassed). The study began mean 77.0 (SEM 10.1) min and 79.5 (12.8) min after aortic clamping, in the control and N_2O groups, respectively. During oxygen–air ventilation, the haemodynamic data were similar in both groups (table I). After nitrous oxide, heart rate (HR), pulmonary capillary wedge pressure (PCWP) and systemic vascular resistance (SVR) were not significantly altered. Mean arterial pressure (MAP) and cardiac index (CI) decreased significantly (by 16.3% and 19%, respectively, $P < 0.05$ within and between groups). No patient experienced any ST–T segment changes during the study.

COMMENT

Our results suggest that moderate concentrations of nitrous oxide decreased cardiac performance during fentanyl anaesthesia after CABG. Previous reports have advocated avoidance of nitrous oxide after CABG because of an increased risk of coronary obstruction by air embolism [5]. The careful purging of grafts in our study, should have minimized, but not totally avoided, coronary air embolism. Moreover, the delay between the anastomoses and the time of the study (more than 75 min) should have allowed clearance of entrapped air from the coronary circulation.

The reduction in myocardial function in this study was marked and is in contrast with the mild depressant effect of nitrous oxide in the isolated heart (LV$dP/dt_{max}$ decreases of 5%) [6]. A decrease in cardiac index (by 19%) whilst ventricular loading conditions and heart rate were unchanged, suggest severe myocardial depression and is similar to previous studies of fentanyl and nitrous oxide given before CABG [1]. This suggests that the depression of cardiac function by nitrous oxide was not enhanced by the presence of an ischaemia–reperfusion injury. However, the use of nitrous oxide immediately after CABG is not recommended.

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CASE REPORTS

ANAESTHESIA IN A PARTURIENT WITH OSTEOGENESIS IMPERFECTA

E. CHO, S. S. DAYAN AND G. F. MARX

SUMMARY

A 20-yr-old primigravida at 38 weeks gestation with premature rupture of membranes and evidence of fetal distress required urgent Caesarean section. The diagnosis of osteogenesis imperfecta had been made 4 days earlier. The patient refused a regional anaesthetic. Difficulties in the administration of general anaesthesia to patients with osteogenesis imperfecta were recognized and managed accordingly. These problems are discussed and the importance of early antenatal assessment of such patients by the department of anaesthesia is emphasized.

KEY WORDS

Anaesthesia: obstetric. Complications: osteogenesis imperfecta.

Osteogenesis imperfecta is an inherited disease of connective tissue that affects bone, sclera and the inner ear. The disease consists of distinct disorders that are transmitted in an autosomal dominant or autosomal recessive fashion. The dominant types appear to be mild, while the recessive types are either severely deforming or lethal in the perinatal period. The prevalence of the disease is 5 per 100000 live births, with a greater incidence in females [1, 2].

CASE REPORT

The anaesthetist on call was informed that a 20-yr-old primigravida had arrived in the Labour Suite with premature rupture of membranes and fetal distress requiring urgent Caesarean section. The presence of osteogenesis imperfecta had been recognized only 4 days earlier.

The patient had received antenatal care in a clinic in which the source of illumination was fluorescent tube lighting. However, at 38 weeks gestation, she had a fetal non-stress test (evaluation of fetal heart rate response to fetal movements over a period of time) in a room with natural light, and her blue sclera was brought to the attention of an obstetrician. An exceedingly short stature (height 124 cm) was noted also. Direct questioning revealed a history of multiple fractures after minor falls during childhood. There were no scoliotic changes. She was referred for genetic counselling but, unfortunately, the department of anaesthesia was not notified.

The patient refused regional anaesthesia for Caesarean section. Premedication was with 30 ml of cooled sodium citrate solution. Positioning on the operating table was undertaken gently; the patient was placed on a cooling blanket in a position of left lateral tilt. Routine monitors were then applied (electrocardiogram, pulse oximeter, peripheral nerve stimulator). Arterial pressure was measured with a manual sphygmomanometer and temperature with an oesophageal stethoscope. Inspired oxygen and end-tidal carbon dioxide concentrations were measured also. Anaesthesia was induced with thiopentone after 5 min of preoxygenation. Vecuronium, rather than suxamethonium, was used for neuromuscular block: a priming dose of 0.015 mg kg^{-1} i.v. was followed 3 min later by 0.05 mg kg^{-1} [3]. Ninety seconds later, tracheal intubation was performed with care and without hyperextension of the neck while cricoid pressure was applied. Anaesthesia was maintained with 0.75% isoflurane in 100 % oxygen until delivery of the infant, at which time the mixture was changed to 40% nitrous oxide and 0.25% isoflurane in oxygen. An infant, small for gestational age, was delivered after 5 min with Apgar scores of 6 and 9 at 1 and 5 min, respectively. The procedure continued uneventfully except for the development of hyperthermia (38.7 °C) which responded to cooling by blanket and cold i.v. solution. Drugs were not required for antagonism of neuromuscular block. The patient underwent smooth recovery, refused further tests and was discharged home on the 6th day postpartum together with her baby who also had blue sclera.

DISCUSSION

Osteogenesis is a rare inherited disease which has been classified into four distinct types. Types II and III are autosomally recessive; they are of no importance to the obstetric anaesthetist, as type II is perinatally fatal and subjects afflicted with type III usually die in childhood from severe kyphoscoliosis. Types I and IV, both autosomally dominant, are characterized by short stature, bone fragility leading to frequent fractures and dentinogenesis resulting in easily broken teeth. While the fractures in type I, the most common of the four disorders, are generally non-deforming, those of type IV tend to cause long-bone and thoracic deformities. Type I is charac-

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terized also by the presence of distinct blue sclera (because of pigmentation showing through thin tissue) and presenile hearing loss from otosclerosis [4, 5]. Mild hyperthermia with excessive diaphoresis is a common feature, but does not appear to be of the malignant type [6]; it is the result of either an abnormal central nervous system temperature regulating mechanism or abnormal cellular energy metabolism [5]. Increased serum thyroxine concentrations associated with increased oxygen consumption occur in at least 50% of patients with the disease [7]. Platelet cell dysfunction because of decreased release of platelet factor is another potential complication [5].

These abnormalities must be considered in the management of anaesthesia. Of special concern is the propensity for developing fractures and broken or dislodged teeth. Care must be taken when moving the patient to and from the operating table, and pressure areas should be well padded. An automated arterial pressure cuff may be hazardous, as overinflation can result in a fracture [7]. Suxamethonium-induced fasciculations may cause fractures, as may hyperextension of the neck, which should be avoided. During laryngoscopy and tracheal intubation, the mandible may be fractured or teeth injured.

There is a tendency for these patients to develop hyperthermia and the temperature should be monitored closely. A cooling blanket should be placed under the patient and cold i.v. solutions be readily available. Increased inhaled oxygen concentration is recommended. Elective surgery should not be undertaken if the patient has a pyrexia before operation [5, 7]. If thoracic deformities are severe, they may be associated with significant mechanical disease causing reduced vital capacity, decreased chest wall compliance and hypoxaemia because of ventilation–perfusion mismatch [2]. Therefore an increased $F\text{I}_{\text{O}_2}$ and decreased tidal volume are recommended. Unusual bleeding caused by platelet abnormalities may require platelet transfusions [5].

Although our patient received general anaesthesia, the best anaesthetic technique is conduction block, as it avoids the necessity for tracheal intubation, makes the development of hyperthermia less likely and facilitates the detection of thyroid storm [6, 8]. For Caesarean section, either spinal or lumbar extradural block may be chosen. In two case reports of parturients with osteogenesis imperfecta undergoing Caesarean section, lumbar extradural block was administered successfully using either 0.5% bupivacaine or 3% chloroprocaine [6, 8]. There is, however, a possibility of technical difficulty if there have been previous fractures of the lumbar spine [8]. Above all, as emphasized by Brennan, Halfacre and Woods [9] in their report of a gravida with porphyria, the importance of early antenatal assessment of these patients by the department of anaesthesia cannot be overstressed.

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CHANGE IN CEREBRAL BLOOD FLOW VELOCITY PATTERN DURING INDUCED HYPOTENSION: A NON-INVASIVE INDICATOR OF INCREASED INTRACRANIAL PRESSURE?

A. M. LAM

SUMMARY

A neurologically intact patient underwent spinal instrumentation under hypotensive anaesthesia 10 days after a mild closed head injury. Transcranial Doppler monitoring of the right middle cerebral artery revealed an abnormal flow pattern, suggesting increased intracranial pressure, impaired autoregulation, or both. Patients with a mild head injury may have altered intracranial haemodynamics and the time course of recovery from these changes is unknown.

KEY WORDS

Brain: blood flow, intracranial pressure. Equipment: transcranial Doppler ultrasonography.

Induced hypotension is used frequently during surgical procedures to reduce blood loss and the risk of cerebral aneurysm rupture. Although the technique is generally safe, inadequate organ perfusion during hypotension is a potential risk, and the brain is one of the most vulnerable organs. However, psychometric studies in healthy young patients have failed to detect any ill effect of induced hypotension on brain function after operation [1]. Many hypotensive agents are vasodilators and may cause increase in intracranial pressure (ICP) in patients with decreased intracranial compliance [2, 3] and induced hypotension is generally contraindicated until the dura is open in such patients. However, decreased intracranial compliance is not always apparent clinically and use of induced hypotension in such patients may cause an increase in ICP and decrease in cerebral perfusion pressure potentially leading to brain ischaemia or brain herniation. A patient with a recent head injury is reported in whom the changes in cerebral blood flow velocity pattern during induced hypotension are consistent with such a possibility.

CASE REPORT

A previously healthy 24-yr-old male suffered a traumatic T10 compression and L1 burst fracture from a motorcycle accident. He was found unconscious at the scene of the accident and his trachea was intubated by the paramedic team before transport to hospital. On arrival a computed tomography scan of his head was normal. He was subsequently taken to the operating room where laparotomy revealed a serosal tear of the right colon, small liver lacerations, contusion of the pancreas and retroperitoneal haematoma. Hemicolectomy was performed, after which he was transferred to the intensive care unit for further management. The next morning he awoke, and when aroused was alert and obeyed commands. His trachea was extubated the following day. His condition continued to improve and, 10 days later, Harrington rod instrumentation was proposed to stabilize his spine. As induced hypotension is routinely used in our institution to minimize blood loss in such procedures, he consented to participate in a clinical trial of adenosine for induced hypotension and intraoperative determination of cerebral blood flow by xenon clearance as well as transcranial Doppler ultrasonography (TCD). The study had been approved previously by the University of Washington Human Subjects Review Committee.

Anaesthesia was induced with fentanyl 5 $\mu g\ kg^{-1}$, thiopental 5 $mg\ kg^{-1}$, vecuronium 0.1 $mg\ kg^{-1}$ and lignocaine 1.5 $mg\ kg^{-1}$. After tracheal intubation, mechanical ventilation was instituted to maintain $P\text{E}'_{CO_2}$ at 4.5–4.8 kPa and anaesthesia was maintained with 0.8% isoflurane (inspired) and 50% nitrous oxide in oxygen. A 16-gauge, 140-mm catheter was inserted retrogradely into the right internal jugular bulb for measurement of cerebral venous oxygen saturation. The patient was then placed prone on a Stryker Frame with the head supported in a neutral position. During stable anaesthesia when arterial pressure was 110/60 mm Hg (mean AP = 76 mm Hg), and $P\text{E}'_{CO_2}$ 5 kPa, xenon-133 20 mCu in saline was injected into the left subclavian vein and CBF measured using the Novo Cerebrograph 10a by xenon washout over 15 min [4] and was found to be 59 ml/100 g min^{-1}. At 7.5 min after injection, simultaneous arterial and cerebral venous blood samples were obtained for measurement of oxygen and haemoglobin content. Arteriovenous oxygen content

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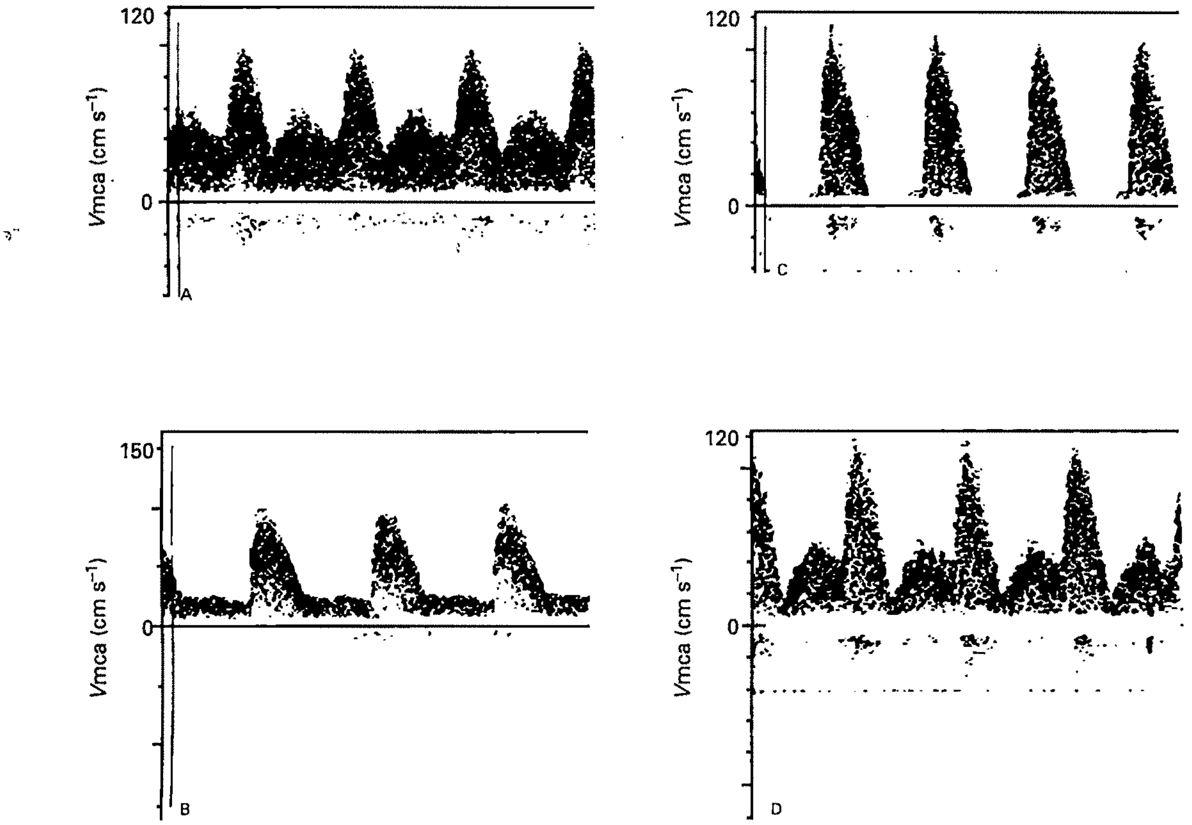

Fig. 1. A: Middle cerebral artery flow (*V*mca) pattern recorded during normotension before induction of hypotension with adenosine. Pulsatility index is normal. B: Flow pattern during adenosine-induced hypotension. (Note change in vertical scale in anticipation of increase in flow velocity.) There is a large decrease in diastolic velocity with corresponding increase in pulsatility index (see table I). C: Flow pattern during accidental washin of adenosine with systemic hypotension and loss of diastolic flow. D: Immediately following recovery of arterial pressure to normotension. An early decrease in diastolic flow is seen, but the flow pattern is otherwise normal.

Table I. *Changes in arterial pressure (AP), right middle cerebral artery mean flow velocity (Vmca), pulsatility index (PI), arteriovenous oxygen content difference* ($Ca_{O_2}-Ca_{O_2}$) *and calculated CBF before, during and after adenosine- and sodium nitroprusside-induced hypotension. The only CBF measured was obtained during the control period, the rest were calculated from proportional changes in Vmca. Adeno. I = Stable hypotension with adenosine. Adeno. II = during termination of adenosine infusion when the deadspace amount was washed in. †No blood samples were obtained during the initial recovery period*

	AP (mm Hg)		*V*mca (cm s^{-1})				
	Sys/Dias	Mean	Sys/Dias	Mean	PI	($Ca_{O_2}-Cv_{O_2}$) (vol %)	CBF (ml/100 g min^{-1})
Control	110/60	76	100/42	61	1.0	3.04	59
Adeno. I	85/37	53	100/20	46	1.7	4.46	44.5
Adeno. II	68/35	46	99/1	34	2.9	5.35	33
Recovery†	115/58	77	120/30	60	1.5		58
Nitroprusside	78/39	52	100/25	50	1.5	5.41	48.4
Recovery	120/60	80	98/35	56	1.13	4.17	54.2

difference ($Ca_{O_2}-Cv_{O_2}$) was calculated from the formula:

$$(Ca_{O_2}-Cv_{O_2}) = \mathrm{Hb} \times 1.39 \times (Sa_{O_2}-Sjv_{O_2}) + (Pa_{O_2}-Pjv_{O_2}) \times 0.003 \text{ vol \%}$$

where Hb = haemoglobin concentration; Sa_{O_2} = arterial oxygen saturation; Sjv_{O_2} = jugular bulb oxygen saturation; Pa_{O_2} = arterial oxygen tension; Pjv_{O_2} = jugular bulb oxygen tension. Oxygen tensions were measured with a Nova automated analyser and the oxygen content calculated from a Severinghaus Blood Gas Calculator. At the end of 15 min of xenon washout, the blood flow velocity of the right middle cerebral artery (*V*mca) was measured using a TCD (Medasonics, Fremont, California) insonated at a depth of 50 mm over the right temporal window [5]. The *V*mca recording during normotension showed a normal flow pattern, with a mean velocity of 61 cm s^{-1} and pulsatility index (systolic velocity − diastolic velocity/mean velocity) of 1.0 (fig. 1A). Hypotension was then induced with an infusion of adenosine 5.3 mg ml^{-1} (Astra Pharmaceuticals, Westborough, Massachusetts), commencing at a rate of 20 µg kg^{-1} min^{-1} and increasing

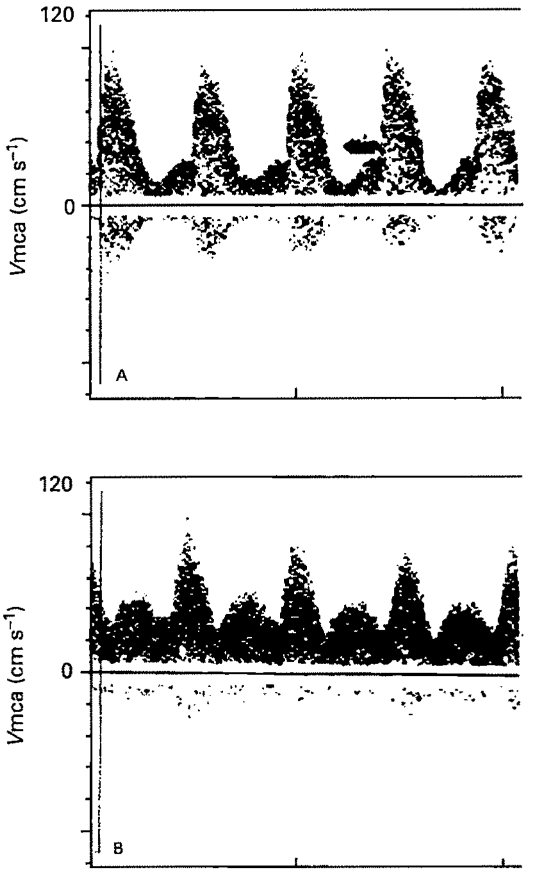

FIG. 2. A: Middle cerebral artery flow (*V*mca) pattern during sodium nitroprusside-induced hypotension. Note the low diastolic flow velocity. B: Normal flow pattern following discontinuation of sodium nitroprusside infusion. Corresponding systemic arterial pressure and metabolic data are displayed in table I.

by 20–40-μg kg^{-1} min^{-1} increments every 30 s to achieve a mean AP of 55 mm Hg. After about 20 min of stable hypotension, an attempt was made to repeat CBF measurement, at which time the Cerebrograph failed and no reading was obtained. Simultaneous arterial and jugular bulb blood-gases were nevertheless obtained. Repeat TCD recording now demonstrated a systolic spike pattern with a very low diastolic velocity (fig. 1B). Blood-gas measurement confirmed an increased $(Ca_{O_2} - Cv_{O_2})$ (table I) and hypotension was discontinued. During the termination of hypotension, adenosine in the i.v. tubing was inadvertently administered and the AP decreased to a mean of 46 mm Hg, at which point TCD showed complete loss of diastolic flow (fig. 1C). This hypotension was less than 1 min in duration and thereafter the TCD reverted to a normal flow pattern (fig. 1D). Because induced hypotension was once again requested by the surgeon, and it was not clear at the time whether the change in flow pattern was related directly to the adenosine or to the AP changes, an infusion of sodium nitroprusside was started. Again, the decrease in diastolic flow velocity occurred (fig. 2A), as did an increase in $(Ca_{O_2} - Cv_{O_2})$ (table I). The sodium nitroprusside infusion was then discontinued and the flow velocity returned to a normal pattern (fig. 2B) and normotension was maintained for the remainder of the surgical procedure. The patient awoke with mild confusion, but was otherwise neurologically intact and was alert 24 h later. The changes in *V*mca and corresponding $(Ca_{O_2} - Cv_{O_2})$ with changes in arterial pressure and hypotensive agents are shown in table I. Cerebral blood flow was obtained only for the control period and all other CBF data displayed in the table for comparison purposes were calculated assuming that change in *V*mca is proportional to change in CBF [6].

DISCUSSION

Patients with severe head injury frequently have increased ICP and impaired ability to autoregulate and are generally not considered to be candidates for induced hypotension, even if the surgical procedure may warrant it. In contrast, patients who have suffered subarachnoid haemorrhage may have similar impairment, but induced hypotension can be used safely, provided the intracranial compartment is decompressed by opening the dura and the lower limit of autoregulation is not exceeded. However, a therapeutic dilemma may occur in a patient who has recovered from a closed head injury with normal neurological status and who presents for a surgical procedure for which induced hypotension is requested. Indeed, in the patient reported, because of the long duration from the original injury (10 days) and a normal neurological status clinically, there was no suspicion that he had residual decreased intracranial compliance, or impaired autoregulation, and yet his response as illustrated by the TCD suggested that one or both of these phenomena may have been present.

TCD was introduced by Aaslid in 1982 as a non-invasive monitor of cerebral haemodynamics and is accepted currently as a useful diagnostic test for cerebral vasospasm [7], intracranial stenosis [8] and confirmation of intracranial circulatory arrest [9]. It is in the context of the last indication that the findings of this case become relevant. Several authors have documented the characteristic progression of TCD pattern as ICP increases towards the systemic arterial pressure and cerebral perfusion pressure correspondingly declines; decrease in early diastolic flow is followed by the development of a systolic spike pattern with complete loss of diastolic flow, progressing to a reverberating or oscillating flow pattern with anterograde flow in systole and retrograde flow during diastole, and eventually complete loss of flow signal [9–11]. The onset of complete loss of diastolic flow or retrograde diastolic flow suggests that the ICP is equal to or exceeds the systemic diastolic pressure. With induced hypotension in this patient, the diastolic flow decreased and the pulsatility index [12] (a mathematical method of quantifying the intracranial stiffness: pulsatility index = systolic velocity − diastolic velocity/mean velocity) increased, suggesting an increase in ICP. When the systemic diastolic pressure was 35 mm Hg, TCD diastolic flow ceased, suggesting that the ICP approached this value. This was accompanied by a decrease in CBF as indicated by the increase in $(Ca_{O_2} - Cv_{O_2})$, although it was still within normal limits. Unfortunately, the Cerebrograph malfunctioned at this point and no confirmatory CBF reading was obtained. Although the calculated CBF and the measured ($Ca_{O_2} - Cv_{O_2}$) at this time remained within acceptable limits, it should be noted that severe hypotension was only transient, the blood-gas tensions were obtained towards the end of the episode and the cerebral metabolic need was reduced by general anaesthesia. Furthermore, the observed TCD flow pattern is indicative of increased cerebrovascular resistance consistent with a decreased intracranial compliance, but not necessarily inadequate flow as high flow and high ICP can co-exist, even if only transiently. This differs from the pattern in patients with severe increases in ICP which progress to an oscillating flow pattern (forward flow during systole and backward flow of the same magnitude during diastole) indicative of intracranial circulatory arrest [10, 11]. The TCD pattern or pulsatility may depend on cerebral perfusion pressure more than on intracranial pressure [11] and the observation may be explained also by a reduction in systemic AP in a patient with pre-existing increased ICP. Neither the normal flow pattern during normotension nor the preoperative clinical condition exclude the possibility of increased ICP.

Adenosine is a potent systemic vasodilator [13], but its effects on cerebral blood flow are uncertain, possibly reflecting species differences [14–16]. In at least one human study, adenosine has been shown to be a cerebral vasodilator [16]. Irrespective of the hypotensive agent used, if autoregulation is intact, systemic hypotension induces cerebral arterial vasodilatation, decreased vascular resistance and increased cerebral blood volume. While this change is physiological in normal subjects, in patients with decreased intracranial compliance a dangerous increase in ICP can occur, and may have been a contributing factor in this patient. That this was not a direct effect of adenosine was confirmed by the development of a similar flow pattern and arteriovenous oxygen content difference when sodium nitroprusside was given subsequently.

For the purpose of comparison, we have tabulated the CBF values during these observations in table I, but with the exception of the control CBF value, which was measured, values were calculated from the change in *V*mca, assuming that the changes in these two variables were proportional. While this assumption has been shown to be valid in studies examining the cerebrovascular response to carbon dioxide and during carotid endarterectomy [6, 17], it may or may not be valid for the conditions pertaining in the present patient, depending on the constancy of the diameter of the middle cerebral artery. Nitroglycerin has been reported to cause a reduction in flow velocity without a change in flow [18]. Such vasodilatation, however, would not cause the observed change in flow pattern with a corresponding increase in pulsatility index. The changes in the ($Ca_{O_2} - Cv_{O_2}$) further support the contention that the changes in mean velocity and CBF were at least qualitatively similar.

This case demonstrates that a patient apparently recovered from a closed head injury, in this instance 10 days from the initial event, may still have impaired intracranial compliance or cerebral elastance, and suggests that induced hypotension should be avoided in such patients. The temporal course of recovery of normal intracranial compliance from an uncomplicated head injury is not known. Routine use of intracranial pressure monitoring would avoid any adverse effects, but its benefits must be balanced against the risk of invasive monitoring with its attendant potential complications. While we are not advocating the routine use of TCD in these patients, it may help to define the indications for ICP monitoring.

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COMMENTARY

EXTRADURAL DIAMORPHINE FOR POSTOPERATIVE ANALGESIA: AUDIT OF A NURSE-ADMINISTERED SERVICE TO 800 PATIENTS IN A DISTRICT GENERAL HOSPITAL

M. E. STUART-TAYLOR, I. S. BILLINGHAM, R. F. BARRETT AND J. J. CHURCH

SUMMARY

We report the use of extradural diamorphine for postoperative analgesia as a nurse-based service on selected surgical wards in a district general hospital. Eight hundred patients received lumbar or thoracic extradural diamorphine analgesia for postoperative or traumatic pain. Diamorphine was administered in bolus form by suitably trained nursing staff. Satisfactory analgesia, recorded on a verbal rating scale at the conclusion of the service, was achieved in 94.6% of patients. The technique was considered by medical and nursing staff to be a safe and acceptable method of analgesia. Respiratory depression, defined as a ventilatory frequency of less than 10 b.p.m., occurred in seven patients (incidence of 0.9%). All occurred in the theatre recovery area or in the intensive care unit. Retrospectively, each was predictable and all responded to naloxone 0.4 mg.

KEY WORDS

Anaesthetic techniques: extradural. Analgesia: postoperative. Analgesics: diamorphine.

The use of extradural opioids for treatment of postoperative pain has been established since Behar, Magora and Olshwang used extradural morphine in 1979 [1]. Initially, excellent results were claimed [2–5] with few side effects, but subsequent reports were less favourable [6, 7]. This has led to the belief that opioids cannot be given safely unless the patient is monitored in an intensive care unit (ICU), thus limiting the number of patients who might benefit from this form of analgesia [8]. The Joint Working Party Report on Postoperative Pain [9] suggested that certain provisions and resources should be made available on designated wards to care for patients receiving extradural opioid analgesia.

This report describes 800 patients given extradural diamorphine, administered by specially trained nursing staff on selected surgical wards. The aim of this prospective study was to audit the efficacy and safety of extradural diamorphine in a district general hospital where only minimal monitoring facilities were available and yet where an effective form of postoperative analgesia could be administered.

PATIENTS AND METHODS

All patients who were to undergo lower limb joint replacement, major abdominal general and gynaecological surgery, and thoraco-abdominal surgery, were visited before operation. After careful explanation by the anaesthetist, extradural diamorphine was offered for postoperative analgesia. This service was also made available to patients suffering from major trauma. Exclusion criteria included patient refusal, anti-coagulant therapy and local or generalized sepsis.

In this audit no attempt was made to standardize anaesthetic technique. The extradural catheter was inserted by the anaesthetist before or after induction of anaesthesia and in most cases local anaesthetic was injected through the catheter as a supplement to general anaesthesia. The first dose of extradural diamorphine was given when the patient had awakened from the general anaesthetic. If local anaesthetic had been given during operation, the trained recovery staff were encouraged to give the first top-up of diamorphine. If the extradural had not been used during operation, the anaesthetist gave the first dose of diamorphine while the patient was in the recovery area. According to the nature of the surgery, the patient was then transferred to the intensive care unit or, after 1 h of observation, returned to the surgical ward where the nursing staff had received training in the use of extradural diamorphine.

Early experience showed that diamorphine 2.5 mg provided acceptable analgesia. Therefore, the top-up dose of diamorphine was prescribed as 2.5 mg diluted in normal saline 10 ml, to be given every 2–3 h as required. For clarification, these instructions were written on a separate drug treatment chart. This was accompanied by a chart on which patient details and ventilatory frequencies were recorded at 30-min intervals throughout the duration of the extradural. Both charts contained prescription for naloxone 0.2 mg to be given i.v. and 0.2 mg i.m. in the

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TABLE I. *Patient characteristics and dosage data*

	Female ($n = 392$)	Male ($n = 408$)	All ($n = 800$)
Age (yr)	62.8 (16–89)	69.4 (24–89)	66.0 (16–89)
No. doses	6.5 (1–30)	4.2 (1–18)	5.3 (1–30)
Total dose (mg)	16.7 (2.5–80)	10.4 (2–45)	13.6 (2.5–80)
Dosage interval (h)	7.8 (2.7–24)	9.1 (3.7–20)	8.5 (2.7–24)
Total duration of extradural analgesia (h)	46.3 (18–150)	38.3 (11–120)	42.2 (11–150)

TABLE II. *Surgical procedures and site of extradurals (ED)*

Surgical classification	Thoracic ED (No.)			Lumbar ED (No.)			Total	
	M	F	Subtotal	M	F	Subtotal	No.	%
Orthopaedic	2	0	2	154	298	452	454	56.75
Upper abdominal	18	2	20	152	84	236	256	32.0
Lower abdominal	0	0	0	22	25	47	47	5.9
Thoracic	12	6	18	2	0	2	20	2.5
Fractured ribs/pelvis	5	1	6	4	3	7	13	1.6
Peripheral/vascular	0	0	0	6	4	10	10	1.25
Total	37	9	46	340	414	754	800	100.00

presence of respiratory depression. Where analgesia was considered by the patient to be inadequate within 20 min of extradural diamorphine, a further top-up could be given within 2 h, after consultation with the anaesthetist. Papaveretum i.m. was prescribed as rescue analgesia if the second top-up dose was found to be ineffective after 1 h, with continued 30-min observation of ventilatory frequency. The patients were visited after operation for assessment of analgesia and to give reassurance to the nursing staff. The on-call anaesthetist was informed of the presence of patients with diamorphine extradurals by a notice board in the anaesthetic department. After removal of an effective extradural, the patient was given oral analgesia. The subjective quality of the analgesia provided was assessed by the patient using verbal rating scale (VRS) (nil, poor, satisfactory, good and excellent). This was recorded on the chart by the nurse. In addition, any side effects such as urinary retention or incontinence, pruritis, nausea and vomiting were recorded.

Ventilatory frequency was recorded for 6 h after the last dose of diamorphine.

Training of nursing staff

Qualified nursing staff attended a lecture on the management of diamorphine extradurals; this included the anatomy and physiology of the extradural space, the pharmacology of local anaesthetics and diamorphine and the top-up procedure. Emphasis was placed on the need for close observation and careful documentation, and the management of respiratory depression.

Our definition of respiratory depression was ventilatory frequency less than 10 b.p.m., in which case the staff were instructed to wake the patient; if this failed to produce an increase in frequency they were to assume that the diamorphine was responsible. The procedure for managing respiratory depression was to administer 40% oxygen via a face mask, to maintain ventilation with positive pressure ventilation if ventilation ceased, to give naloxone as prescribed, and to contact the anaesthetist on call. The staff witnessed two top-ups and administered two top-ups under observation before being allowed to practise independently.

TABLE III. *Quality of analgesia assessed by verbal rating scale (VRS)*

VRS	Patients scoring No.	%
Excellent	287	35.9
Good	294	36.75
Satisfactory	176	22.0
Poor	38	4.75
Nil	5	0.6
Total	800	100.00

RESULTS

The patients' ages, sex distribution and dose of extradural diamorphine are shown in table I.

The types of surgical procedures and site of insertion of the extradural catheter are shown in table II.

Satisfactory analgesia was achieved in 94.6% of patients (table III).

Of the 43 patients in whom adequate analgesia was not achieved, nine (20.9%) had received thoracic extradurals (table IV).

The incidence of side effects is shown in table IV. Of the 800 patients, 174 (21.75%) were catheterized before surgery. Difficulty in voiding requiring catheterization occurred in another 93 patients (14.85%). The relationship between type of surgery and side effects is shown in table V. In 139 patients (17.4%) there was one side effect only. Fifteen patients (1.9%) experienced two side effects.

TABLE IV. *Incidence of side effects. †Identified as patients not catheterized for surgical reasons*

	Patients experiencing	
	No.	%
Inadequate analgesia	43	5.4
Urinary retention†	93	14.85
Nausea or vomiting	7	0.9
Pruritis	22	2.75
Use of naloxone	7	0.9
Total	172	24.8

There were seven patients who required naloxone. All had lumbar extradurals (table VI).

DISCUSSION

We have shown that a nurse-administered service for topping up diamorphine extradurals can be established safely on designated surgical wards in a district general hospital. The study represents the largest series reported on the use of postoperative extradural diamorphine. A wide range of patients have benefited from a form of postoperative analgesia which could not have been offered if observation in an intensive or high care unit was obligatory.

The analgesia achieved in more than 94% of patients was described by them as satisfactory or better. Of those who felt that analgesia was less than satisfactory, more than 20% had received thoracic extradurals. It has been shown in other studies that analgesic requirements are greater after thoracic operations, but there is also a greater risk of respiratory depression when opioids are used in the thoracic extradural space. From experience in this study, we feel that bupivacaine offers better analgesia for thoracic extradurals. This finding has been supported by Torda and colleagues [10].

The incidence of urinary retention in this study is comparable to that of others using extradural morphine [11, 12]. Of those patients who reported nausea or vomiting, 0.9% (seven patients) had undergone orthopaedic procedures, and it was felt that prophylactic antiemetic treatment was unnecessary. Nausea occurred within 30 min of the extradural diamorphine top-up. This incidence is similar to that in Jacobsen and colleagues' study [13], in which both i.m. and extradural diamorphine were associated with an incidence of nausea of 36%.

Pruritis occurred in 22 patients (2.75%). Lanz and others [14] demonstrated a dose-dependent relationship, and the low incidence seen in our study is probably accounted for by the low dose of diamorphine used.

There was an initial reluctance by the nursing staff to accept a new analgesic technique. However, this was overcome by the ease of administration, the necessarily close observation of the patients and the low incidence of respiratory depression and other side effects. The benefit to the patient of closer monitoring by the nurses on the ward ensured frequent appraisal of pain relief and analgesic requirement. This may not have occurred if i.m. opioids were given.

The Royal College of Nursing views the practice of topping-up extradurals as an extension of the nursing role, requiring a recognized period of training and a proven level of competence. In Salisbury, a certificate of competence was issued to every nurse completing the training. A survey of qualified hospital nursing staff showed support for the concept of a nurse-based extradural analgesic service. In fact, most of those interviewed felt that such training should be compulsory [15].

Early experience demonstrated that, if respiratory depression were to occur, it would be seen whilst the patient was still in the postoperative recovery area and that it would develop gradually over the course of 1 h. Our postoperative facilities, as in many district general hospitals, do not include individual patient pulse oximeters and therefore we instituted half-hourly observation of ventilatory frequency, which also forms part of the recommendations of the Joint Working Party Report on Postoperative Pain [9]. Of the seven cases of respiratory depression, all occurred in the recovery area or in the intensive care unit and within 1 h of the patient receiving diamorphine. The first two patients received more than the recommended dose of extradural diamorphine. No respiratory depression was seen subsequently with the usual dose of 2.5 mg in these patients. All other patients received the standard dose. In the next three patients, interaction with opioids given either as premedication or during operation was assumed to be the cause of respiratory depression. In each instance, depression was reversed rapidly and completely by naloxone, with no adverse effect on analgesia. This emphasizes the need to observe these patients in the recovery area for at least 1 h after the first top-up, and before discharging the patient to the ward. The sixth patient with respiratory depression had a long history of respiratory disease requiring steroid therapy and had undergone ventilation for 3 days when one dose of naloxone was needed during

TABLE V. *Side effects and type of surgery (No. patients). †Number of thoracic extradurals*

Surgical classification	Inadequate analgesia	Urinary retention	Nausea or vomiting	Pruritis	Use of naloxone
Orthopaedic	9	76	7	18	4
Upper abdominal	25 (6)†	8	0	3	3
Lower abdominal	4	4	0	0	0
Thoracic	5 (3)†	2	0	1	0
Fractured ribs/pelvis	0	1	0	0	0
Peripheral vascular	0	2	0	0	0
Total	43	93	7	22	7

TABLE VI. *Summary of patients requiring naloxone. ED = Extradural diamorphine; GA = general anaesthesia*

Patient no.	Sex	Age (yr)	Operation	Before op.	During op.	After op.
1	M	64	Elective aortic aneurysm repair	Premed: Lorazepam 1 mg	Papaveretum 10 mg 2 h after premed	1st dose ED 5 mg 70 min after papaveretum. 2nd dose ED 4 mg 8 h later. Naloxone needed within 1 h of 2nd dose. Subsequent doses of ED 2.5 mg well tolerated
2	F	78	Abdomino-perineal resection	Premed: Lorazepam 1 mg	ED 5 mg given 3 h after premed (at end of 2 h GA)	Naloxone given 45 min after ED. Subsequent doses of ED 2.5 mg tolerated well
3	F	61	Total hip replacement	Premed: Papaveretum 20 mg Hyoscine 0.4 mg	ED 2.5 mg 1 h after premed	Naloxone given after reversal of GA 130 min after intraoperative ED. Subsequent ED tolerated well
4	F	64	Total hip replacement	Premed: Lorazepam 2 mg	Fentanyl 250 μg given 2 h after premed	Doxapram given 1 h after fentanyl. ED 2.5 mg given 30 min later. Naloxone given 25 min later. Subsequent ED tolerated well
5	F	81	Total hip replacement	No premed	Fentanyl 100 μg	ED 2.5 mg given 100 min after fentanyl. Naloxone given after 30 min. ED repeated 4 h later; naloxone needed within 1 h. Papaveretum 10 mg given 5 h later. Naloxone needed 6 h later
6	M	70	Emergency aortic aneurysm repair			IPPV required for 3 days. Naloxone given once during weaning phase. ED tolerated well following this
7	F	71	Total knee replacement	No premed	Inadvertent dural puncture during 1st extradural. 2nd extradural successful	Respiratory depression after 1st ED 2.5 mg. Good response to naloxone. Extradural removed

weaning from ventilation. The seventh patient illustrates the risk of respiratory depression with extradural opioids following dural puncture.

We believe that the following recommendations should be included with those of the Working Party with regard to the use of extradural diamorphine:

(1) Preoperative opioids should be avoided [16].

(2) The use of opioids during operation should be avoided by the use of local anaesthetic agents via the extradural catheter.

(3) A dose of diamorphine 2.5 mg should not be exceeded.

(4) The use of extradural opioids after dural puncture should be avoided.

With these precautions, it is our opinion that the management of patients receiving extradural diamorphine top-ups in surgical wards is safe, provided that the first dose is given in the recovery area and that the patient is observed there for a minimum of 1 h or in the ICU. An adequate level of ward staffing has not been established in our hospital, but the nurse in charge of the ward is given notice of the return of a patient with an extradural *in situ*, and the option of declining to use the extradural route if the quantity and quality of nursing staff is not available.

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ABSTRACTS

PROCEEDINGS OF THE ANAESTHETIC RESEARCH SOCIETY

CAMBRIDGE MEETING

NOVEMBER 22–23, 1991

(The name of the author presenting the paper is shown in bold type. * Indicates non-member.)

All authors have certified that, where appropriate, studies have been conducted with the approval of the relevant Human Ethics Committee or Animal Experimental Review Committee.

OXYGEN DELIVERY AND CONSUMPTION IN PATIENTS UNDERGOING ELECTIVE SURGERY FOR ABDOMINAL AORTIC REPAIR

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Oxygen delivery ($D\mathrm{o}_2$), oxygen consumption ($\dot{V}\mathrm{o}_2$), mixed venous saturation ($S\mathrm{v}_{\mathrm{O}_2}$) and arterial concentrations of lactate were studied in patients undergoing elective abdominal aortic repair.

Seven male patients aged 72–81 yr were premedicated with temazepam and metoclopramide. A peripheral venous line, a radial arterial line and pulmonary artery flotation catheter were inserted under local anaesthesia. $D\mathrm{o}_2$, $\dot{V}\mathrm{o}_2$, $S\mathrm{v}_{\mathrm{O}_2}$ and lactate concentrations were measured while the patients were awake (I), 15 min after induction of anaesthesia, 15 min after aortic cross-clamping, during suture of the abdomen and 1 h after recovery from anaesthesia (awake (II)).

Anaesthesia was induced with etomidate 0.3–0.4 mg kg^{-1}, fentanyl 1–2 μg kg^{-1}, and muscle relaxation was provided by pancuronium 0.1 mg kg^{-1}. After tracheal intubation, anaesthesia was maintained with 67% nitrous oxide in oxygen and 0.5–1% isoflurane. Ventilation was adjusted to maintain end-tidal carbon dioxide between 4.5 and 5.0 kPa. Inspired oxygen tension was adjusted to maintain arterial $P\mathrm{o}_2$ greater than 12.5 kPa. Central venous pressure was maintained between 8 and 10 mm Hg, using crystalloids and colloids throughout the procedure. An increment of fentanyl 1 μg kg^{-1} was administered before abdominal incision.

Repeated measures analysis of variance was used to assess changes over time.

The results of the study are shown in table I.

$\dot{V}\mathrm{o}_2$ decreased in all patients during anaesthesia with isoflurane. This decrease was independent of any change in $D\mathrm{o}_2$. Since $S\mathrm{v}_{\mathrm{O}_2}$ was increased throughout anaesthesia, $D\mathrm{o}_2$ appeared to be adequate for the patient's metabolic requirements.

HYPOXAEMIA AND PAIN RELIEF AFTER UPPER ABDOMINAL SURGERY

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A major factor limiting the spread of patient controlled analgesia (PCA) is the fear of respiratory depression. The aim of this study was to compare the respiratory effects of PCA and i.m. analgesia after upper abdominal surgery using a computerized system of analysis and display of continuous $S\mathrm{a}_{\mathrm{O}_2}$ monitoring described previously [1].

Thirty-nine patients undergoing upper abdominal surgery were monitored continuously the night before and for 24 h immediately after surgery whilst breathing air. After a standardized general anaesthetic, patients were allocated randomly to receive i.m. analgesia (morphine 0.15 mg kg^{-1} prn) or PCA (i.v. morphine 1 mg bolus, 5 min lockout time, no background infusion). VAS scores for pain were obtained 4-hourly and patients were asked to rate their pain relief verbally at 24 h as poor, fair, adequate or excellent.

There was no significant difference in the mean age, degree of obesity, male, female distribution, duration of surgery, blood loss or dose of morphine between the two groups. A higher proportion of patients in the PCA group (48%) rated their analgesia as excellent compared with the i.m. group (10%) ($P < 0.05$). This was associated with significantly lower pain scores in the PCA group at 12, 16 and 24 h after operation. Hypoxaemia (defined as $S\mathrm{a}_{\mathrm{O}_2} < 94\%$ for more than 12 min h^{-1} [2]) occurred in both treatment groups before operation (6/20 i.m., 3/19 PCA patients) and in the postoperative period (12/20 i.m., 8/19 PCA patients). In the i.m. group, there was a significant increase in the time patients' $S\mathrm{a}_{\mathrm{O}_2}$ values were less than 94% (25 min h^{-1}) in the postoperative period compared with preoperative values (12.5 min h^{-1}) ($P < 0.05$). Severe hypoxaemia ($S\mathrm{a}_{\mathrm{O}_2} < 85\%$ for more than 6 min h^{-1}) was observed in three patients receiving i.m. analgesia and in one patient receiving PCA. The three patients with severe hypoxaemia in the i.m. group had no evidence of preoperative hypoxaemia but developed an unstable and de-

TABLE I. *Mean (95% confidence limits) oxygen transport variables and lactate concentrations measured while the patients were awake (I), 15 min after induction of anaesthesia (Postind.), 15 min after aortic cross-clamping (Cross on), during suture of the abdomen (Clamp off) and 1 h after recovery from anaesthesia (Awake II).* **$P < 0.01$; ***$P < 0.001$; ****$P < 0.0001$

	Awake I	Postind.	Cross on	Clamp off	Awake II
$\dot{V}\mathrm{o}_2$ (ml min^{-1})	138 (106–181)	87 (71–106)	81 (66–99)	95 (79–113)	167 (134–209)****
$D\mathrm{o}_2$ (ml min^{-1})	456 (398–513)	424 (255–592)	373 (262–484)	428 (335–522)	516 (412–619)
$S\mathrm{v}_{\mathrm{O}_2}$ (%)	67 (58–75)	77 (69–85)	78 (73–84)	77 (73–81)	67 (63–71)***
Lactate	0.44 (0.3–0.6)	0.70 (0.3–1.1)	0.50 (0.3–0.8)	1.31 (0.6–1.9)	0.79 (0.5–1.0)**

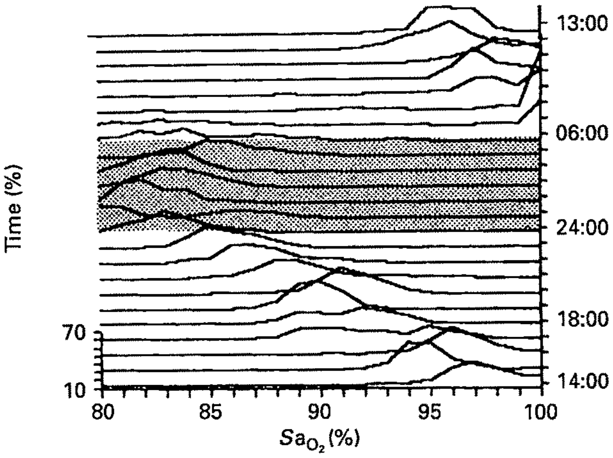

FIG. 1. Pattern of severe hypoxaemia (Sa_{O_2} < 85%) in the postoperative period in three patients receiving i.m. analgesia.

teriorating pattern of hypoxaemia in the postoperative period (fig. 1)

The use of PCA was associated with improved pain relief compared with i.m. analgesia with no increase in postoperative hypoxaemia.

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HYPOXAEMIA AND PAIN RELIEF AFTER LOWER ABDOMINAL SURGERY

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In a previous study comparing i.m., patient controlled (PCA) and extradural opiate analgesia, all three methods resulted in satisfactory analgesia [1]. However, bolus extradural diamorphine produced postoperative hypoxaemia for longer periods than the other two methods. In the present study, an extradural bolus was compared with an extradural infusion and PCA with a shorter lockout period.

The study was approved by the hospital medical Ethics Committee and written informed consent was obtained from 50 ASA I and II patients undergoing elective abdominal hysterectomy. After premedication with a benzodiazepine and induction of general anaesthesia, a lumbar extradural was established with 0.5% bupivacaine 15–20 ml. The patients were allocated randomly to receive extradural analgesia or PCA after operation. Twenty patients received an extradural bolus of diamorphine 3.6 mg in 9 ml of 0.9% saline administered on request by the patient. Ten of these patients had participated in a previous study [1]. Twenty patients received an extradural infusion of 0.15% bupivacaine with 0.01% diamorphine 4–6 ml h^{-1}. Ten patients self-administered i.v. diamorphine at a maximum rate of 1 mg every 5 min. In each case the total dose of diamorphine received in the first 24 h after operation was recorded. Continuous monitoring of arterial oxygen saturation was performed the night before operation and for 24 h after operation [1]. Pain scores were obtained every 4 h after operation using a 100-mm visual analogue scale (VAS). In addition, patients were asked to give an overall assessment of their postoperative analgesia at 24 h using a verbal score; poor, fair, adequate and excellent. Side effects were noted.

The three treatment groups did not differ significantly in age or degree of obesity. The dose of diamorphine used by the patients with PCA was significantly greater than the patients with extradural analgesia ($P < 0.001$). Hypoxaemia was defined as a Sa_{O_2} value below 94% for more than 20% of each epoch (i.e. > 12 min h^{-1} [2]). According to these criteria five of the patients in the extradural infusion group were hypoxaemic during the preoperative monitoring period. After operation, 9/20, 11/20 and 2/10 patients receiving an extradural bolus, extradural infusion and PCA, respectively, were hypoxaemic. The extradural infusion group had longer periods with Sa_{O_2} values below 94% before operation compared with the other two groups ($P < 0.05$). After operation, the time that patients' Sa_{O_2} values were less than 94% was greater for the extradural infusion group compared with the extradural bolus group ($P < 0.05$). Five patients in the extradural infusion group spent more than 10% of the postoperative monitoring period with Sa_{O_2} values below 90%. Only one of these patients had been hypoxaemic before operation. No patient in either of the other groups spent 10% of the postoperative period with Sa_{O_2} values less than 90% ($P < 0.05$). At 24 h after surgery, 75% of the extradural and 90% of the PCA patients considered their postoperative analgesia to be excellent. Patients with extradural infusions had significantly lower pain scores at 12 to 24 h after operation compared with the other two groups ($P < 0.05$). More patients experienced severe nausea or vomiting in the PCA group than in the extradural infusion group ($P < 0.05$).

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NASAL OXYGEN PREVENTS HYPOXAEMIA THE NIGHT AFTER UPPER ABDOMINAL SURGERY

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Pulse oximetry has demonstrated episodic hypoxaemia in patients breathing air after abdominal surgery, particularly in association with disturbed ventilatory patterns during sleep [1]. Studies in which patients were given oxygen therapy have suggested that frequent or prolonged episodes of hypoxaemia may occur still [2]. Most previous studies relied on the automated logging of oxygen saturation measurements from patients who were not observed continuously. However, when oxygen saturation was logged during the maintenance of anaesthesia, 6% of the measurements were considered to be false, of uncertain validity or absent [3].

We studied 15 ASA I–III patients (nine male, six female; median age 64 yr, range 43–75 yr) undergoing upper abdominal surgery. No patient had severely limiting respiratory disease. All patients were anaesthetized with thiopentone or propofol, a muscle relaxant, nitrous oxide and a volatile agent, with or without morphine or diamorphine. In eight patients, a thoracic extradural catheter was inserted before induction of anaesthesia and an infusion of bupivacaine and diamorphine was given for postoperative analgesia. The other seven patients received morphine or diamorphine by i.v. PCA. Patients were studied for 6 h, between 23:00 and 05:00 approximately, and all received oxygen 2 litre min^{-1} by nasal cannulae. Seven patients were studied the night before operation and all 15 patients during the night after operation. Sp_{O_2} (Ohmeda Biox 3700 with finger probe), gas flow and carbon dioxide at the nose, rib cage and abdominal movements (respiratory inductance plethysmograph), ECG (CM5) and external oblique muscle EMG were measured continuously in all patients. Oesophageal and gastric pressures were also measured in some patients after operation. An anaesthetist was present throughout the monitoring period and noted whether any Sp_{O_2} readings of less than 90% appeared to be artefactual (associated with patient movement, poor or absent plethysmographic waveform or probe displacement).

Abnormal ventilatory patterns were common after operation, particularly partial upper airway obstruction and phasic abdominal muscle activity. The former also occurred before operation in several patients, especially when supine.

There were 14 occasions when Sp_{O_2} readings were less than 90%, but these appeared to be artefactual. On three of these occasions, the oximeter probe position was adjusted. Apart from these episodes, there were no Sp_{O_2} readings less than 90% in any patient before or after operation.

Oxygen 2 litre min^{-1} by nasal cannulae may prevent episodic hypoxaemia (Sp_{O_2} < 90%) the night after upper abdominal surgery in patients without severe respiratory disease receiving analgesia by extradural infusion or i.v. PCA.

The automated Sp_{O_2} readings from an oximeter, without observation of the patient or oximeter to detect artefacts, or the simultaneous recording of a measure of signal quality, is incapable of distinguishing episodes of desaturation from artefact.

Abnormal patterns of ventilation are common the night after upper abdominal surgery but some of the abnormalities are also present before surgery.

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POSTOPERATIVE HYPOXAEMIA: AN ANALYSIS OF CAUSATIVE FACTORS

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Impaired gas exchange and ventilatory control are responsible for the majority of cases of postoperative hypoxaemia [1]. We demonstrated how the former can amplify the effects of the latter by varying the inspired oxygen pressure (PI_{O_2}) and using pulse oximetry to measure arterial oxygen saturation (Sp_{O_2}).

We studied 20 ASA I–III patients (mean age 52.5 yr, range 26–82 yr; mean weight 72.9 kg, range 45–139 kg) undergoing major surgery. Continuous oximetry was performed during the night before operation and for the first three days and nights after operation, using an Ohmeda Biox 3700 interfaced with a Toshiba IBM portable PC for data storage. In addition, the quasistatic relationship between PI_{O_2} and Sp_{O_2} was determined before operation, and 1, 15 and 30 h after operation. Several different inspired oxygen pressures were produced, in a step-wise fashion, by mixing nitrogen and oxygen in differing proportions using a Y-tube connection and fed to a tightly fitting Venturi mask. The inspired oxygen pressure was measured using an Ohmeda Oxycap gas analyser, calibrated against known gas mixtures, sampling from just in front of the patient's lips.

Compared with a stable preoperative pattern of Sp_{O_2} when breathing air, a much more unstable pattern was a common finding in the early postoperative period and was often observed in awake patients. The curve relating PI_{O_2} to Sp_{O_2} altered in the postoperative period with both downward and lateral displacements. The downward displacements could be described by a model incorporating venous admixture and the lateral displacement by an increased inspired to alveolar Po_2 gradient. The lateral displacement, with respect to the position of the oxyhaemoglobin dissociation curve, changed from mean 5.5 (95% confidence intervals 4.3–6–8) kPa before operation to 10.1 (8.2–12.0) kPa after operation. This finding was statistically significant ($P = 0.0003$, analysis of variance). This difference remained highly significant over the whole study period. The downward displacement was not altered at 1 h after operation but was increased at 15 h ($P = 0.0414$) and at 30 h ($P = 0.0586$).

We believe this finding explains the instability of the Sp_{O_2} pattern seen in the postoperative period. When the PI_{O_2} lay on the steep part of the PI_{O_2} *vs* Sp_{O_2} curve hypoxaemia was observed and the pattern of oxygen saturation showed a marked instability, whereas a PI_{O_2} on the plateau of the curve resulted in a stable pattern (fig. 2). Patients with a marked vertical downward displacement of the curve, as a result of a large shunt, and whose PI_{O_2} was still on the flat part of the curve were hypoxaemic but showed a stable pattern of Sp_{O_2}. The shape and position of the PI_{O_2} *vs* Sp_{O_2} curve is a descriptor of gas exchange and changes in this relationship are important determinants of postoperative hypoxaemia.

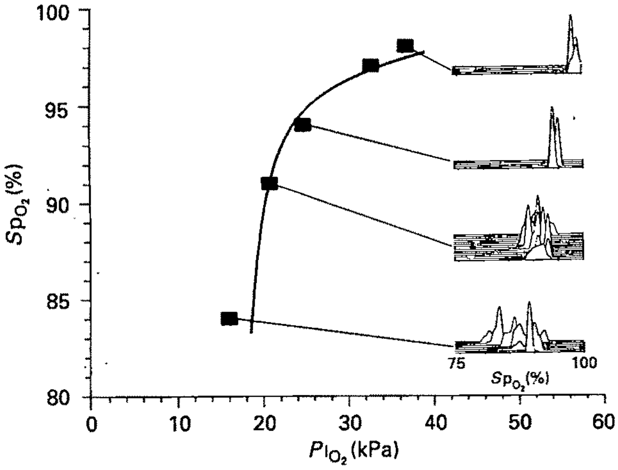

FIG. 2. Relationship of inspired oxygen pressure (PI_{O_2}) to oxygen saturation (Sp_{O_2}) and the pattern of Sp_{O_2} in the postoperative period.

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WHAT'S IN A SLOPE? COMPARISON OF CARBON DIOXIDE SINGLE BREATH TESTS IN CHILDREN WITH INTRACARDIAC SHUNTS

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The slope of phase III of the carbon dioxide single breath test (SBT-CO_2) [1] is a measure of the spread of ventilation/perfusion ($\dot{V}/\dot{Q}$) ratios. Children with normal pulmonary circulation have minimal alveolar deadspace and a rather flat phase III. In right–left shunting, phase III appears to be unusually flat, although there may be a large alveolar deadspace. Pulmonary overcirculation as a result of left–right shunting may cause a marked increase in phase III slope, which must be associated with increased spread of $\dot{V}/\dot{Q}$ ratios [2]. Radiologists can observe "pulmonary hyperinflation" in such lesions, possibly suggesting increased expiratory resistance, and this also suggests increased $\dot{V}/\dot{Q}$ spread.

SBT-CO_2 was obtained during routine monitoring of 68 children undergoing cardiac surgery. The children were anaesthetized with nitrous oxide in oxygen and fentanyl, with or without halothane. On the basis of preoperative investigations (angiography, echocardiography), the patients were divided in to four groups: normal pulmonary circulation (N), pure right–left shunts (RL), pure left–right shunts (LR), and those with mixed shunts (RLLR). The slope of phase III was obtained by measuring the difference in the height of the curve at expired volumes equivalent to 5% and 10% of predicted total lung capacity. This figure was divided by the mean height of the curve between the two points to correct for hyperventilation.

Groups N and LR were significantly older (mean age 5 yr) than the other two groups (1.2 yr). Group LR had significantly steeper phase III slopes than the similarly aged group N ($P < 0.01$).

TABLE II. *Mean* (SD) *phase III slopes of the carbon dioxide single breath test in children with normal pulmonary circulation (group N), pure right–left shunts (group RL), pure left–right shunts (group LR) and those with mixed shunts (group RLLR)*

	Group N	Group LR	Group RL	Group RLLR
n	12	16	23	17
Weight (kg)	19.3 (9.4)	16.2 (7.6)	10.3 (5.0)	8.4 (3.7)
Slope	0.041 (0.014)	0.059 (0.014)	0.039 (0.018)	0.062 (0.021)

Group RLLR had significantly steeper phase III slopes than the similarly aged group RL ($P < 0.01$) (table II).

At different ages varying proportions of total lung capacity are ventilated; in this study about 14% at 1 yr, and 9% at 5 yr. Therefore, it may be difficult to compare slopes in group N with those in the much younger RL group; however there did not appear to be any significant differences between the two groups.

The significant increase in phase III slope in children with LR shunting can be attributed to an increased spread of $\dot{V}/\dot{Q}$ ratios. This is presumably caused by an abnormal pulmonary circulation; all the children in this group had two- or threefold increases in pulmonary flow, and in many cases increased pulmonary artery pressures. When LR and RL shunting occur in combination, phase III slope is as steep as in pure LR shunting; the effects of increased pulmonary flow appear to dominate the $\dot{V}/\dot{Q}$ pattern.

In pure RL shunting, phase III slope is not "supernormal", as the eye would have it; the lower level of $F\text{CO}_2$ in these children is perhaps deceptive. The flat phase III suggests that alveolar gas exchange is good, any alveolar deadspace being solely as a result of RL shunting.

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CENTRAL NON-INVASIVE PULSE OXIMETRY USING RETINAL OXIMETRY: A FEASIBILITY STUDY

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The aim of the study was to develop a central non-invasive retinal pulse oximeter for monitoring during anaesthesia. The retinal artery is a branch of the internal carotid artery and oxygen saturation of the retinal artery may reflect internal carotid saturation and therefore cerebral oxygenation. The haptic contact lenses, the first contact lenses developed in 1888, were designed to protect the cornea. These lenses have been modified by many researchers to perform different tasks.

A method of reflectance oximetry was used in which both the incident and reflected light traverses the eye via its natural pupil. A special haptic contact lens was made to focus light in the plane of the pupil so that the amount of incident light reaching the retina was substantially independent of pupil size. A screened support carrier on the front of the haptic lens contained the fibreoptic/LED probes. The experiments were conducted in two phases: *in vitro* with a model eye and *in vivo* in patients undergoing general anaesthesia. The LED probes used for the *in vitro* experiments used two wavelengths, 660 nm and 850 nm; in the anaesthetized patients a specially modified Nellcor 100 oximeter was used.

Seven patients (six Caucasians, one Negroid; four males; mean age 62.5 yr (range 42–72 yr)) were included in the study. All patients received relaxant anaesthesia for general and gynaecological surgery. Depending on the surgical procedure, recordings were made with the lens *in situ* for up to 1 h.

In the *in vitro* experiments, a reliable correlation between the ratio of reflected red (660 nm) and infra-red (850 nm) light and oxygen saturation from 60% to 100% saturation in stored blood was produced, although this was not linear below 60% saturation. In the anaesthetized patients, a red and infra-red signal was obtained in six of seven patients. The pupil diameter in these patients varied between 1.5 and 3 mm, and systolic blood pressure between 80 and 140 mm Hg. The next day none of the patients could tell which eye had been used for the study, and there were no clinical signs of corneal damage. It was not possible to obtain recordings in one patient (a Caucasian) due to excess movement.

The *in vitro* experiments with the model eye show that it is possible to use reflectance oximetry to obtain a linear relationship between the ratio of red/infra-red light and oxygen saturation, at least to 60% saturation. It may mean also that it is possible to use the device to calibrate the pulse oximeter.

The *in vivo* results indicate that with this lens it is possible to use reflectance retinal oximetry in anaesthetized patients, irrespective of pupil size.

TABLE III. *Mean* (SEM) *time (min) to TOF ratios of 0.25, 0.5, 0.75 and 0.95 in the rectus abdominis and hypothenar muscles*

TOF ratio	Rectus abdominis	Hypothenar muscles	*P* value
0.25	39 (3)	51 (4)	< 0.001
0.50	48 (3)	59 (5)	< 0.01
0.75	56 (4)	72 (6)	< 0.001
0.95	69 (5)	88 (8)	< 0.01

EFFECTS OF ATRACURIUM ON ABDOMINAL MUSCLES

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Depth of neuromuscular block is monitored usually on hand muscles by stimulating the ulnar nerve. Extrapolation to the degree of relaxation of other muscles is based on this response. However, other muscle groups have been shown to differ in their onset and recovery responses to non-depolarizing muscle relaxants [1, 2]. Since abdominal muscle relaxation is important in certain types of surgery, we compared the effects of atracurium on the rectus abdominis and hand muscles.

After Ethics Committee approval was obtained, 11 ASA I or II adult patients undergoing non-abdominal surgery were studied. Anaesthesia was induced with thiopentone 3–5 mg kg^{-1} and maintained with nitrous oxide and isoflurane in oxygen. Supramaximal train-of-four (TOF) stimulation to the ulnar nerve was monitored on a Datex Relaxograph. Two surface electrodes were placed in the 10th intercostal space near the anterior axillary line. When stimulated, the EMG response was measured on a Tektronix 5103N oscilloscope via three surface electrodes placed over the long axis of the rectus abdominis. After administration of atracurium 0.5 mg kg^{-1}, time to maximal twitch depression was measured on both muscles. Times to TOF ratios of 0.25, 0.5, 0.75 and 0.95 were calculated. Statistical comparisons were made using the Student's paired t test.

Mean age (SEM) was 40 (6) yr and mean weight 67 (3) kg. Time to maximum twitch depression was 2.4 (0.3) min at the hand and 1.6 (0.2) min at the rectus abdominis ($P < 0.001$). Recovery from paralysis occurred earlier at the rectus abdominis in all patients. The time to TOF ratios in the rectus abdominis and hypothenar muscles are shown in table III.

The onset of an intubating dose of atracurium was faster at the rectus abdominis than at the hand. This effect has been observed in other muscle groups [1, 2], and is probably because of the closer proximity of the abdominal muscles to the central circulation and the larger blood flow. Recovery of neuromuscular transmission occurs sooner at the rectus abdominis. Residual paralysis is therefore more likely to be detected if hand muscles are monitored. However, recovery of neuromuscular function may have occurred at abdominal muscles when minimal response to ulnar nerve stimulation is apparent at the hand.

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CLEARANCE OF ATRACURIUM IN VOLUNTEERS UNDER ACID AND ALKALINE CONDITIONS

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The elimination of atracurium is dependent partly on spontaneous degradation to laudanosine in physiological conditions (Hofmann degradation). Nevertheless, little is known of the effects of modification of extracellular pH on the elimination of atracurium in normal subjects.

We studied the pharmacokinetics of atracurium in acid and alkaline conditions in a crossover study in nine healthy male

TABLE IV. *Mean* (SEM *(confidence limits)) pharmacokinetics of atracurium in acid and alkaline conditions*

	V^{ss} (ml kg^{-1})	*Cl* (ml kg^{-1} min^{-1})	$T_{\frac{1}{2}}^{\beta}$ (min)
Acid	156.1 (8.6) (139.2–173.0)	7.8 (0.3) (7.1–8.4)	14.9 (1.3) (12.4–17.4)
Alkaline	164.7 (14.2) (136.7–192.6)	9.6 (0.8) (8.0–11.3)	12.4 (0.7) (11.0–13.8)

volunteers. A systemic acidosis or alkalosis was produced on separate occasions by the oral administration of ammonium chloride 12 g or sodium bicarbonate 18 g in divided doses during the 12 h preceding the study. At the start of each study, control samples of blood and urine were obtained. Atracurium 0.05 mg kg^{-1} i.v. was then administered and blood samples obtained at 2, 4, 6, 8, 10, 15, 20, 30, 45, 60, 75, 90, 120 and 180 min from the opposite arm. The bladder was emptied again at 90 min, and the pH and volume of both samples of urine were measured. Concentrations of atracurium in plasma and urine were determined by HPLC [1]. Pharmacokinetic variables were derived by standard non-compartmental methods [2].

In all subjects, atracurium was removed rapidly from plasma in a biexponential manner and the drug was not detected in plasma after 75–90 min. The volume of distribution at steady state (V^{ss}) was similar in acid and alkaline conditions, but the mean clearance (*Cl*) of atracurium was approximately 20% greater in alkaline conditions (table IV). In all volunteers, clearance was greater and the half-life value ($T_{\frac{1}{2}}^{\beta}$) was less than in anaesthetized patients [1]. In acid conditions, the urinary *Cl* of unchanged atracurium was mean 1.1 (SEM 0.1) ml kg^{-1} min^{-1}, 14.3(2.0)% of the total systemic clearance of the drug. Values for urinary *Cl* were slightly less than glomerular filtration rate. No unchanged atracurium was present in alkaline urine.

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PHARMACOKINETICS OF THE MONOQUATERNARY ALCOHOL METABOLITE OF ATRACURIUM

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Atracurium is eliminated partly by ester hydrolysis to a monoquaternary alcohol (MQA) and an acid. This study was designed to investigate the pharmacokinetics of the MQA metabolite of atracurium, and to assess the relative importance of ester hydrolysis in the elimination of the drug.

We studied the pharmacokinetics of atracurium in acid and alkaline conditions in seven healthy male volunteers. A systemic acidosis or alkalosis was produced on two separate occasions by the oral administration of ammonium chloride 12 g or sodium bicarbonate 18 g in divided doses during the 12 h preceding each study. At the start of each experiment, control samples of blood and urine were obtained. Atracurium 0.05 mg kg^{-1} i.v. was then administered and blood samples obtained at 2, 4, 6, 8, 10, 15, 20, 30, 45, 60, 75, 90, 120 and 180 min from the opposite arm. The bladder was emptied again at 90 min, and the pH and volume of both samples of urine were measured. Concentrations of the MQA in plasma and urine were measured by HPLC [1], and pharmacokinetic variables were determined by standard methods [2].

In all volunteers, plasma concentrations of the MQA were maximal within 5–10 min, and rapidly decreased within 60–90 min. In alkaline conditions, mean plasma concentrations of the MQA were approximately 30% higher than in acid conditions, and the terminal half-life value was slightly longer (mean 39.9 (SEM 6.6) min *vs* 32.1 (7.6) min). The apparent urinary clearance of the MQA was approximately five times greater in acid conditions (2.03 (0.27) ml min^{-1} kg^{-1} *vs* 0.44 (0.04) ml min^{-1} kg^{-1}), presumably because of the breakdown of the MQA at pH 8. These results were interpreted in terms of the predicted biological behaviour of the MQA and are consistent with the elimination of 50–70% of atracurium as the MQA.

After administration of atracurium, the MQA is rapidly cleared from plasma. The apparent urinary clearance of the MQA is approximately five times greater in acid than in alkaline conditions. The results are consistent with the concept that ester hydrolysis is a significant route of elimination of atracurium [3].

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PHARMACOKINETIC–PHARMACODYNAMIC MODELLING OF SUXAMETHONIUM

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COMPARISON OF ATROPINE AND GLYCOPYRROLATE AS ANTAGONISTS TO NEOSTIGMINE IN ISOLATED HUMAN TAENIA COLI

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The use of neostigmine may encourage the dehiscence of bowel anastomosis [1]. Few studies have investigated the relative protective effects of different cholinergic antagonists; Child [2] suggested that there was no difference between atropine and glycopyrrolate.

After local research Ethics Committee approval, isolated strips of human taenia coli were obtained from 33 operative specimens of descending or sigmoid colon. The specimens were obtained fresh in theatre, and were the result of elective surgery for tumour. Normal segments of taenia coli were mounted as strip preparations under isometric conditions in a tissue bath containing physiological saline with the following ionic composition (mmol litre^{-1}): Na^+ 134, K^+ 4.5, Mg^{2+} 1.2, Ca^{2+} 2.5, Cl^- 119, HCO_3^- 22, SO_4^{2-} 1.2, PO_4^{2-} 1.2. The following organic substrates were also present (mmol litre^{-1}): glucose 11, glucuronate 0.16, citrate 0.16, glutamate 0.06, pyruvate 0.09, ascorbate 0.05, aspartate 0.03. Saline was maintained at 37 ± 0.5 °C and gassed with a 5% carbon dioxide, 95% oxygen mixture. Statistical analysis was performed by one-way and two-way analysis of variance as appropriate, using the SPSS-PC package.

Initial experiments demonstrated that as the concentration of neostigmine was increased the dose–response curve to acetylcholine altered, shifting to the left as expected, but becoming flattened in its central portion. Experiments were conducted in the presence of hexamethonium (10^{-6} mol litre^{-1}), lignocaine (3×10^{-6} mol litre^{-1}) or tetrodotoxin (TTX) (3×10^{-7} mol litre^{-1}) to test whether this observation was the result of preganglionic activation of postganglionic fibres. Compared with curves obtained in the absence of the drug, neither hexamethonium nor TTX had a statistically significant effect on the dose–response curve to acetylcholine, although the shape of the curve altered in the presence of TTX. In the presence of lignocaine, the dose–response curve to acetylcholine was a more normal shape and shifted to the right compared with the control ($P < 0.01$).

In a further series of 20 experiments, inhibitory dose–response curves to atropine or glycopyrrolate were constructed in the presence of acetylcholine (3×10^{-5} mol litre^{-1}) and neostigmine (3×10^{-6} mol litre^{-1}), in the presence or absence of TTX (3×10^{-7} mol litre^{-1}). The presence of TTX had no significant effect upon the position or shape of the inhibitory curves. The bath concentration of atropine producing 50% inhibition of the response to acetylcholine (3×10^{-5} mol litre^{-1}) was 5.0 ×

TABLE V. *Reversal characteristics of three different doses of neostigmine (20, 40 and 80 μg kg*$^{-1}$*) administered at two levels of spontaneous recovery (5–10% and 40–50% recovery). Values are median (range)*

Neostigmine (μg kg^{-1})	Recovery index (min) (T1 = 0.25–0.75)	Time (min) from neostigmine to	
		T1 = 0.75	TOF = 0.7
5–10% recovery			
20 ($n = 9$)	4.2 (3.1–7.5)	6.4 (4.1–10.1)	11.3 (9.3–15.7)
40 ($n = 9$)	2.3 (1.2–7.2)	3.9 (2.3–9.4)	8.3 (4.1–13.3)
80 ($n = 9$)	1.0 (0.4–4.0)	1.9 (1.0–6.2)	5.2 (3.0–14.0)
40–50% recovery			
20 ($n = 10$)	—	1.8 (1.0–3.2)	4.5 (3.0–8.0)
40 ($n = 10$)	—	1.3 (0.8–2.6)	3.0 (2.2–5.2)
80 ($n = 10$)	—	1.2 (0.8–3.0)	2.3 (1.3–3.7)

10^{-7} mol litre^{-1}. The equivalent concentration of glycopyrrolate was 1.4×10^{-7} mol litre^{-1}.

If neostigmine plays a part in anastomotic dehiscence, then the *in vitro* data suggest that glycopyrrolate may provide better protection.

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ATRACURIUM REVERSAL: WHAT IS THE OPTIMUM DOSE OF NEOSTIGMINE?

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The optimum dose of neostigmine for antagonizing atracurium block has yet to be defined. A previous study demonstrated that it is inadvisable to reduce the dose of neostigmine even when there is considerable spontaneous recovery from vecuronium [1]. The aim of the current study was to establish an optimum dose-range of neostigmine when antagonizing atracurium.

We investigated 57 adult patients during enflurane anaesthesia as described previously [1]. In 27 patients neostigmine was given when the EMG had recovered to 5–10% of control. These patients were allocated randomly into three groups ($n = 9$) to receive neostigmine 20 μg kg^{-1}, 40 μg kg^{-1} or 80 μg kg^{-1}. The remaining 30 patients were randomized into three groups ($n = 10$) in a similar manner and received the same doses of neostigmine, but only after spontaneous recovery had progressed to 40–50% of control. The EMG ultimately achieved 90–110% of control in all patients and an accepted correction factor for drift was applied [2].

Differences between groups were analysed using the Kruskal–Wallis test followed by pair-wise comparisons using the Mann–Whitney U test with Bonferroni's correction for multiple comparisons. $P < 0.05$ was considered significant.

At 5–10% spontaneous recovery the recovery index was progressively decreased by increasing doses of neostigmine from 20 μg kg^{-1} to 80 μg kg^{-1}. The train-of-four (TOF) ratio reached 0.7 more rapidly after 40 μg kg^{-1} compared with 20 μg kg^{-1} but there was no benefit in increasing the dose to 80 μg kg^{-1} (table V).

At 40–50% spontaneous recovery there were no differences between dose groups in the time taken to reach 75% recovery. Reducing the dose of neostigmine from 40 μg kg^{-1} to 20 μg kg^{-1} did not significantly prolong reversal to a TOF ratio of 0.7, but increasing the dose to 80 μg kg^{-1} tended to accelerate reversal ($P = 0.07$) (table VI).

At 5–10% spontaneous recovery there appeared to be little benefit in giving a large dose of neostigmine (80 μg kg^{-1}). When spontaneous recovery reaches 40–50%, the dose of neostigmine may be reduced from 40 μg kg^{-1} to 20 μg kg^{-1} without prolonging reversal significantly.

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PERIOPERATIVE NEUROMUSCULAR MONITORING AND RESIDUAL CURARIZATION

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Train-of-four (TOF) pattern of stimulation is used widely clinically to quantify the degree of intraoperative neuromuscular block without prior establishment of a control response. A TOF ratio of great than 70% correlates with criteria of adequate clinical recovery [1]. Using these criteria and TOF ratio, some investigators have found the incidence of postoperative residual curarization after pancuronium to be unacceptably high [2]. However, it has recently been suggested that perioperative neuromuscular monitoring is not useful in reducing this incidence [3]. This study examines the influence of manual TOF assessment on the frequency or degree of postoperative residual curarization.

After obtaining institutional approval and written informed consent, we studied 39 ASA I or II patients undergoing abdominal surgery. Patients were free from neuromuscular disease and were not taking any drugs that might influence neuromuscular function.

After premedication with diazepam, anaesthesia was induced with sodium thiopentone 4–6 mg kg^{-1} and fentanyl 4–8 μg kg^{-1}, and maintained with 66% nitrous oxide in oxygen, 0.75% enflurane inspired concentration and increments of fentanyl or sodium thiopentone. The anaesthetist participating in the study had adequate experience with the use of relaxants and monitoring the TOF response. Pancuronium was used to facilitate tracheal intubation and maintain surgical relaxation. On a random basis, doses were titrated either guided by the response to TOF stimulation to achieve and maintain 1–2 responses until the time of antagonism (group A, $n = 20$), or based on clinical criteria (group B, $n = 19$).

Approximately 20 min after antagonism of neuromuscular block, a blinded investigator assessed the recovery in the post-anaesthesia care unit both electromyographically (TOF ratio) and clinically (head lift, adequate cough, hand grip). The groups were compared for frequency and degree of postoperative residual curarization. Data were analysed using Student's t test, and the chi-square test ($P < 0.05$ was considered significant).

Groups A and B were comparable in age, sex, weight and duration of operation. The mean TOF ratio was less in group B (76%) than in group A (88%). The incidence of postoperative residual curarization, as defined by a TOF ratio of 70% or less, was significantly greater in group B (47%) than group A (15%). The incidence of postoperative residual curarization, as defined by clinical criteria, was greater in group B (16%) than in group A (5%).

The use of perioperative TOF monitoring appears to decrease the incidence of pancuronium-induced postoperative residual curarization.

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EFFECT OF ANAESTHETIC DOSES OF PROPOFOL ON LIVER CELL MEMBRANE LIPID PEROXIDATION IN THE RAT

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Vitamin E, a lipid soluble free radical scavenger, constitutes an important component of the antioxidant defences of the cell membrane lipid bilayer. We have demonstrated recently *in vitro* that 2, 6-diisopropylphenol, which is chemically similar to vitamin E, is a potent free radical scavenger [1]. In the present *ex vivo* study we have examined whether anaesthetic doses of propofol contribute to cell membrane antioxidant defences.

In-house bred rats weighing 100–150 g, were used in the study. A 24-gauge cannula was sited in a dorsal tail vein and the animals allocated to receive either a bolus dose of propofol 10 mg kg^{-1} or equivalent volumes of 10 % Intralipid or isotonic saline ($n = 5$ in each group). Two minutes after injection the animals were killed and liver microsomal suspensions prepared. Lipid peroxidation was induced in these membrane systems by adding an Fe^{2+}–ADP/NADPH mixture and the rate of these oxygen consuming reactions monitored with an oxygen electrode mounted in the base of the reaction chamber.

As shown in figure 3, pretreatment with propofol, but not Intralipid or saline, delayed the onset of lipid peroxidation in the membrane preparation. Overall, the mean delay in the evolution of the maximum rate of lipid peroxidation was significantly greater in the propofol pretreated group (mean 15.7 min (SD 2.4 min)) compared with the saline (5.7 (3.5) min, 95 % confidence interval of the difference (CI) 8.6–21.8 min, $P < 0.01$) and Intralipid (2.7 (2.4) min, 95 % CI 14.3–24.8 min, $P < 0.001$) groups.

We conclude that an anaesthetic bolus dose of propofol, but not Intralipid or saline, significantly attenuates the sensitivity of liver cell membranes to free radical mediated lipid peroxidation.

ACKNOWLEDGEMENT

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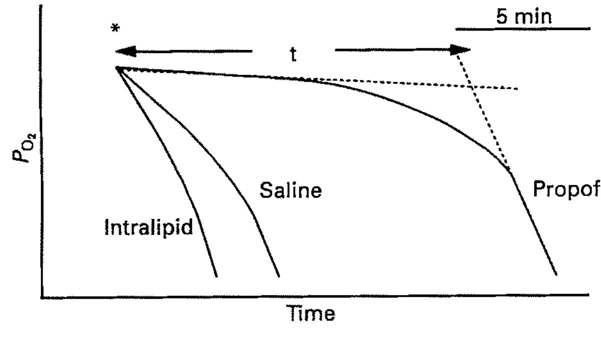

FIG. 3. The rate of lipid peroxidation (Po_2) induced by the addition of Fe^{2+}–ADP/NADPH (*) in rat liver cell membranes pretreated with propofol, Intralipid or saline. The mean delay (t) in the evolution of the maximum rate of lipid peroxidation was greater in the propofol pretreated group.

A SURVEY OF ANAESTHETIC LOG BOOK PRACTICE IN THE NORTH-WESTERN REGION

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Anaesthetic log books have been in existence for many years. The College of Anaesthetists has endorsed their usage recently. Knowledge of their popularity, benefits and downfalls has never been investigated. This study acts as a preliminary forum to evaluate those properties.

All grades of anaesthetists except consultant were sent a brief postal survey. Results returned in a stamped addressed envelope were analysed using a Lotus 123 spreadsheet. Log book systems analysed were of the college, Lancaster, Abbot, computer or self-made types.

Total responders (147) were 63 % of the total questioned (234) with SHOs and registrars representing the bulk of responders (77 %).

The likelihood of keeping any form of log decreased with anaesthetic experience and seniority of grade. Juniors working in non-teaching hospitals were more likely to keep a log. Log type used was very dependant on grade.

Higher grades felt that a lower percentage of cases (i.e. < 75 %) made it into their log books. Using the college book or computer record methods seemed to ensure a higher proportion of cases were recorded.

Actual information recorded varied, however, with logging of ITU experience low (44 %). Recording of regional techniques was 96 %. Review of logged information collected was extremely low. Most anaesthetists (> 65 %) merely glanced at their data.

Responders were asked three direct questions to assess the ability of their system to yield data about experience. All forms of log keeping showed greatly increased ability to quantify anaesthetic experience. Using a computer record provided the most accurate data. Keeping a Lancaster, college or Abbott log book seemed to result in an increased ability to yield accurate data. Very few responders (17 %) felt that a log book had ever helped them to seek training in under experienced fields. Overall about 50 % of the responders found keeping log books enjoyable or useful.

Many responders felt that presentation of the log book to the anaesthetic department and job interviews was a good idea. Presentation at examinations was not as popular. Most felt (85 %) that administration should not be able to gauge clinical activity from anaesthetists' log books.

With career progression 32 % felt they would give up their log upon gaining a senior registrar post whereas less than 50 % said they would continue the practice as a consultant.

UPPER OESOPHAGEAL SPHINCTER PRESSURE AND THE EFFECT OF CRICOID PRESSURE

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LARYNGOSCOPE BLADE POSITION USING A MATHEMATICAL MODEL

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Previous work has demonstrated the effect of blade shape on forward space [1]. Limited forward space is the most common cause of difficult intubation and can be modelled mathematically [2]. This paper describes the interplay between blade shape and modelled anatomical factors. In figure 4, the four airway points are: I, upper incisors; T, hyoid; J, mid-point between mandibular condyles; S, mid-point of mandibular symphysis menti (buccal surface). Blade points I′ and T′ overlap I and T, respectively, when the blade contacts both upper incisors and hyoid. Optimal laryngoscopy requires blade tip–hyoid contact [3]. When forward space is not limiting, favourable blade positions are modelled by anterior rotation about the hyoid point T. As forward space becomes restricted, the blade touches the upper incisors. Subsequently, only posterior rotation about the incisor point I is possible. These rotations are described by the angles ITI′ and

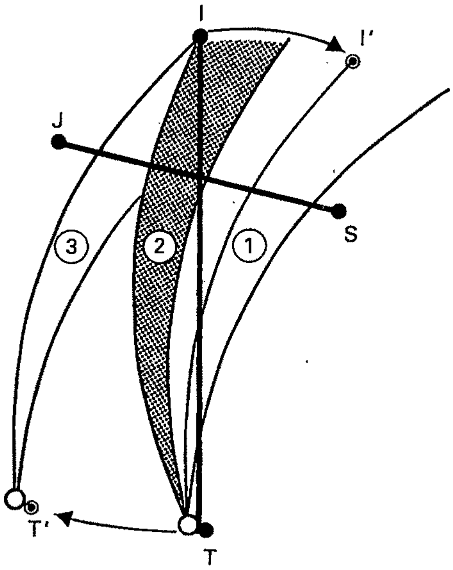

FIG. 4. Laryngoscope blade rotation modelling restricted forward space. (Reference points are described in the text.) Position 1 is when little or no restriction occurs and is modelled by forward rotation about T (ITI′ > 0, TIT′ = 0). In position 2, the blade cannot move off the incisors (ITI′ = 0, TIT′ = 0) but there is still contact with the hyoid and the view remains satisfactory. Position 3 represents critical forward space restriction, with no hyoid contact and loss of view.

TIT′. Angular deviation of the eyeline is measured from I relative to IT [1].

Accurate 1:1 scale photographs were used for modelling. Blade cut outs were positioned on the IT/JS framework. Forward space reduction was simulated by moving S progressively closer to J. Eyeline, ITI′ and TIT′ were measured for each blade position.

The eyeline angle remains small until incisor contact (i.e. ITI′ = O). Thereafter, further forward space restriction moves the blade tip off the hyoid point when TIT′ and eyeline deviation increase proportionally. The forward space enhancing property of curved blades is very evident.

Receding mandible is the most intuitive situation to model, but other difficult intubation factors are easily simulated. The model provides a meaningful comparison for different blade shapes in various anatomical settings.

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EFFECT OF THE LARYNGEAL MASK AIRWAY ON THE LOWER OESOPHAGEAL SPHINCTER DURING ANAESTHESIA

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Regurgitation of gastric contents associated with use of the laryngeal mask airway (LMA) has been reported [1, 2]. The major barrier to passive regurgitation is accepted generally to be the lower oesophageal sphincter (LOS). We have measured LOS barrier pressure during general anaesthesia administered via LMA or face mask in spontaneously breathing patients during surgery.

Twenty-six unpremedicated ASA I–II patients (10 female), aged 20–70 yr, undergoing body surface surgery were studied. Obese patients, those taking drugs affecting LOS pressure, a history of upper abdominal surgery, hiatus hernia, oesophageal reflux, peptic ulceration or diabetes were excluded.

LOS pressures were measured using a slow pull through technique [3] with a 3-mm diameter orogastric probe, containing subminiature strain gauge pressure transducers (Gaeltec Ltd) and displayed on a chart recorder (Biox Z105).

Anaesthesia was induced with thiopentone 5 mg kg^{-1} and fentanyl 1 µg kg^{-1} and maintained with 1.5% halothane and 66% nitrous oxide in oxygen administered via a face mask and Guedal airway. After 10 min, the pressure probe was passed into the stomach; 15 min later, a baseline LOS pressure was recorded. The probe was then reintroduced.

Patients were allocated randomly before anaesthesia to continue at this time with either a face mask and Guedal airway or a LMA of appropriate size. The latter was inserted by an experienced anaesthetist and the cuff inflated with the recommended volume of air. After a further 15 min, a second recording of LOS pressure was made in both groups.

All pressure recordings were analysed by a blinded observer. LOS barrier pressure was taken as the difference between end-expiratory LOS and gastric pressures [3].

Data were tested for normality and analysed using Student's *t* test.

Mean (SEM) percentage change in LOS barrier pressure was +10.8 (7.6)% in the face mask/Guedal airway group and −14.2 (7.6) % in the LMA group ($P = 0.028$).

These data suggest that LOS barrier pressure may be reduced after insertion of a LMA during anaesthesia with spontaneous ventilation.

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PRESSURE EXERTED BY THE LARYNGEAL MASK AIRWAY ON THE PHARYNGEAL MUCOSA

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The laryngeal mask airway (LMA) has a cuff which creates an end-to-end seal between the mask and the larynx. The pressure exerted by this cuff on the pharynx was estimated.

Informed consent was obtained from 10 adult male patients. The pilot tube of each size 4 LMA was connected to a pressure transducer (Spectramed P10EZ) and VSM recorder (Physio Control). The LMA was evacuated to an end-point negative pressure of 20 mm Hg using a 50-ml syringe. The pressure values ($P1$) were recorded for each mask cuff with incremental inflation of air 2 ml to a total of 40 ml. Anaesthesia was induced with propofol 3 mg kg^{-1}, and maintained with spontaneous ventilation of halothane with 67% nitrous oxide in oxygen. The LMA was inserted and the pressure values recorded with incremental cuff inflation ($P2$), and then again with deflation ($P3$) at the end of anaesthesia. The cuff was evacuated to the same end-point and the end-volume recorded. The LMA was removed and pressure values ($P4$) recorded again with incremental cuff deflation. A Cardiocap (Datex) was used to analyse the gas removed from the cuff.

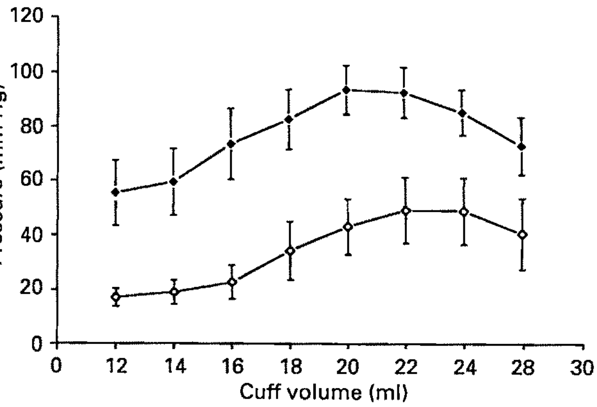

FIG. 5. Calculated mean (SE) pharyngeal mucosal pressures for the start (Pms, ◆) and end (Pme, ◇) of anaesthesia.

Cuff volumes were calculated from injected volumes [1]. The pressure exerted on the pharyngeal mucosa at each cuff volume was calculated for the start (Pms) and end (Pme) of anaesthesia: $Pms = P2 - P1$; $Pme = P3 - P4$. The pressure–volume curves for the $P1$, $P2$, $P3$ and $P4$ values were analysed using analysis of variance for repeated measures. Results are expressed as mean (SE).

The Pms at a cuff volume of 22 ml was 91.9 (9.33) mm Hg, and the Pme was 48.6 (12.01) mm Hg. Values were obtained over the range of cuff volumes (fig. 5).

The mean duration of anaesthesia was 41.5 min (range 15–75 min). Cuff volume increased by 6.2 (0.62) ml. The final nitrous oxide and carbon dioxide concentrations were 13.1 (1.59) % and 2.59 (0.21) %, respectively.

The size 4 LMA appears to exert a substantial pressure on the pharyngeal mucosa which decreases with time *in situ*. This decrease was not caused by a change in compliance of the cuff itself ($P1$ *vs* $P2$, ns).

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MEASUREMENT OF VOICE WAVELENGTH VARIABILITY IN PATIENTS AFTER TRACHEAL EXTUBATION FOR INTENSIVE CARE

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It is well recognized that intubation of the trachea causes damage to the vocal cords [1, 2]. We have used a voice analysis technique presented previously to the Society [3] to analyse voice recordings of intensive care unit patients after tracheal extubation, and compared these with a database of normal voice recordings, taken over 6 consecutive days at the same time each day. The voice recording was of a single monotone note sung for 5 s; this was recorded via a two-channel professional standard recorder (Marantz CP230). The first channel recorded via a microphone, the second via an accelerometer taped to the suprasternal notch.

Ethics Committee approval was obtained. Where possible a voice recording was made before admission to the intensive care unit. To date we have studied 40 patients of whom 23 have been suitable for analysis. A record of progress, level of sedation and time of extubation was made. As soon as possible after extubation the patient was asked to make a voice recording onto tape. Assessments of throat soreness and hoarseness were made with each recording. Recordings were taken for 5 consecutive days after the patient was extubated, at the same time each day. Mean intubation time in the 23 patients was 48.13 h (SEM 8.53 h; median 44 h; range 5–91 h).

An oscilloscope recording of the voice waveform was entered into a specially programmed computer (Dell 316SX), with a 2-kHz filter. The interval between each peak was measured, and a histogram made of the number of times each measured interval occurred. The variability of wavelength of the voice was measured as the spread between the 10th and 90th centile, measured in ms. Separate analyses were made for accelerometer and microphone waveforms.

The microphone data are shown in table VI, for normal and intensive care patients. Day 0 is the first recording for the normal subjects and the preintubation recording of the intensive care patients. Similar data were obtained from the accelerometer recordings.

TABLE VI. *Median (range) wavelength variability (ms), using a microphone, for normal subjects* (n = 8) *and intensive care (ITU) patients* (n = 23)

Day	Normal subjects	ITU patients
0	0.175 (0.05–0.4)	0.25 (0.1–0.6)
1	0.125 (0.05–0.25)	1.5 (0.2–5.4)
2	0.15 (0.1–0.2)	0.8 (0.2–4.0)
3	0.15 (0.1–0.6)	0.5 (0.05–2.4)
4	0.125 (0.1–0.35)	0.5 (0.12–2.4)
5	0.2 (0.05–0.45)	0.35 (0.1–0.85)

We found that there was increased variability in the wavelength of the voice associated with intubation in the intensive care unit. In this preliminary study, however, there was no correlation between variability and mode of sedation or other factors.

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EFFECT OF CARDIOPULMONARY BYPASS ON PLASMA CHOLINESTERASE

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Plasma concentrations of cholinesterase are thought to be decreased by cardiopulmonary bypass (CPB) procedures. The duration of this decrease is in dispute, however, with estimates ranging from 2–7 days [1, 2]. In addition, previous studies involved only patients undergoing hypothermic techniques who were receiving drugs known to be metabolized by plasma cholinesterase. We investigated plasma concentrations of cholinesterase in patients undergoing hypothermic CPB compared with patients undergoing normothermic CPB using drugs not metabolized by plasma cholinesterase.

Fifteen patients undergoing elective open heart surgery were included in the study. Nine patients were undergoing coronary artery bypass grafting under normothermic CPB (group A) and six were having valve replacement surgery under hypothermic CPB (group B). All patients were premedicated with papaveretum 10–20 mg i.m. 1 h before operation. Anaesthesia was induced with fentanyl 10–20 $\mu g\ kg^{-1}$, propofol 1.5–2.5 $mg\ kg^{-1}$ and vecuronium 0.15 $mg\ kg^{-1}$, and maintained with a constant infusion of propofol 3–8 $mg\ kg^{-1}\ h^{-1}$ whilst the lungs were ventilated with 50% oxygen in air. In all cases the bypass circuit was primed with Hartmann's solution 2.5 litre and pump flow was 2.4 $litre\ min^{-1}\ m^{-2}$ at 37 °C and 1.8 $litre\ min^{-1}\ m^{-2}$ at 28 °C. Cobe membrane oxygenators (IF CML) were used throughout, with alpha stat pH management. No blood was added to the circuit during CPB. In group A, myocardial protection was achieved with continuous warm blood cardioplegia while in group B intermittent cold block cardioplegia was used. At the end of CPB, pump blood was transfused as indicated to maintain cardiovascular stability and in the postoperative period blood and fresh frozen plasma were given as required.

Blood for plasma cholinesterase assay was obtained preinduction, 15 min postinduction, pre-CPB, 30 and 60 min after the start of CPB, 30 min after the end of CPB, 60 min after the end of CPB and 1, 2, 5 and 7 days after operation.

Plasma concentrations of cholinesterase were determined using a colorimetric method with butyrylthiocholine as substrate (BM test combination kit) [3]. BM Precinorm E control sera was used as a quality control.

Data were analysed using the Student's unpaired *t* test.

There was no statistical difference between group A and group B with regard to patient characteristics, cross-clamp and bypass times, fresh frozen plasma and blood requirements, or total volume of crystalloid administered during CPB. In addition, there were no statistical differences between the groups in plasma cholinesterase concentrations at any of the sampling times. There was, however, a significant decrease in mean plasma concentrations of cholinesterase with the onset of CPB in both groups: group A from mean 5784 (SEM 323) to 2471 (387) iu $litre^{-1}$; group B from 5641 (325) to 2319 (255) iu $litre^{-1}$ ($P < 0.001$ in both cases). Plasma concentrations of cholinesterase remained significantly lower than preinduction values throughout the 7-day study period in both groups. In three patients sampled at 6 weeks post-CPB, plasma concentrations of cholinesterase had returned to preoperative values.

Plasma concentrations of cholinesterase decreased to approximately 40% of preinduction values with the onset of CPB and remained at this level for at least 7 days with both hypo- and normothermic CPB.

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HAEMODYNAMIC EFFECTS OF TRANSURETHRAL PROSTATECTOMY

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A large retrospective study by Roos and colleagues has suggested an increased mortality after transurethral prostatectomy (TURP) compared with open operation; the relative risk of death in the 5 yr after operation was 1.45 compared to open prostatectomy [1]. This was associated with an increased risk of death from myocardial infarction. Evans and colleagues have studied the changes in cardiac output (CO) during TURP under general anaesthesia. They showed a progressive decrease in CO (maximum 29 %) from the start of resection to the end of surgery [2] and suggested this was a possible mechanism for the greater mortality.

In the present study, we have used the BoMed NCCOM3 impedance cardiograph to investigate haemodynamic changes in patients undergoing TURP during general or spinal anaesthesia. Twenty-two patients (11 undergoing general anaesthesia) were included in the study after premedication with an oral dose of temazepam 20 mg. The two anaesthetic techniques were standardized: thiopentone 4 mg kg^{-1}, fentanyl 100 μg kg^{-1}, vecuronium 0.1 mg kg^{-1} and 0.5–1 % enflurane or 0.5% hyperbaric bupivacaine 2.5–3 ml. General and spinal anaesthesia groups were matched for age, ASA status, duration of resection and weight of gland resected. All patients received Ringer's sodium lactate 1000 ml after induction of anaesthesia.

Heart rate (HR), mean arterial pressure (MAP), CO and thoracic fluid index (TFI) were measured on the ward after premedication and in the anaesthetic room; the mean of these two readings was taken as the baseline value. The intrasubject coefficient of variation (CV) for CO has been shown previously to be between 2.6 and 9.7% [3]. The haemodynamic variables were measured also during induction of anaesthesia, after positioning in theatre, after cystoscopy, at 2, 10, 15, 20, 25, 40, 50 and 60 min during resection, and after 30 min in recovery.

Data were analysed by ANOVA, and values are expressed as mean (SD).

Baseline haemodynamic values did not differ between the two groups. Analysis of all data showed differences in CO with time ($F = 1.76$; $P = 0.0375$). In the general anaesthesia group, there was a time-related decrease in CO ($F = 2.098$; $P = 0.0124$) which occurred after induction of anaesthesia and persisted into the resection period. The maximum decrease from baseline was 1.99 (0.96) litre min^{-1}. Similar changes were seen for HR and MAP. TFI was unchanged. In the spinal anaesthesia group, there were no time-related changes in any of the other haemodynamic variables; the maximum decrease in CO from baseline was 0.77 (0.63) litre min^{-1} ($P < 0.002$ *vs* general anaesthesia group). The range of blood loss estimates was not different between the general and spinal anaesthesia groups. The postoperative serum sodium values were all within normal limits.

In contrast to Evans and Colleagues [2], we found no significant reduction in CO during the period of resection. However, these data suggest that the choice of anaesthetic technique may influence haemodynamic changes during TURP.

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EFFECTS OF AMILORIDE ON THE *IN VITRO* RESPONSE OF MALIGNANT HYPERTHERMIA MUSCLE TO HALOTHANE

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It is generally believed that the most likely cause of malignant hyperthermia (MH) susceptibility is a defect in the calcium release channel of the sarcoplasmic reticulum (SR). This explanation, however, fails to account for the influence of the extracellular calcium concentration [1] and some L-type calcium channel blocking drugs [2] on the *in vitro* responses of MH muscle. The potassium-sparing diuretic amiloride, has been shown to affect sarcolemmal calcium flux in cardiac muscle [3]. We have examined the contribution of amiloride-sensitive mechanisms to the contracture development of *in vitro* MH skeletal muscle fascicles exposed to halothane.

Muscle specimens used were surplus to diagnostic contracture study requirements. The contracture response to incremental additions of 0.5%, 1%, and 2% halothane was recorded in the presence of amiloride 0.5, 1 or 2 mmol litre^{-1}. These responses were compared to those obtained during the diagnostic contracture tests for halothane. Muscle from a further group of patients were used for a second halothane contracture study in the absence of amiloride to ensure that the results were not caused by variability in response between specimens.

Figure 6 shows the contracture responses (mean and 95% confidence intervals (CI)) to incremental additions of 0.5%, 1% and 2% halothane in the presence of amiloride 0.5, 1 or 2 mmol litre^{-1}, and in the absence of amiloride (control). In the presence of amiloride 1 mmol litre^{-1} the force of contracture produced at the threshold concentration of halothane was significantly less than the control (two-tailed paired *t* test: mean difference 0.61 g, 95% CI = 0.286–0.934 g; $P = 0.0192$ with Bonferroni correction). There was no significant difference at amiloride 0.5 or 2 mmol litre^{-1}.

The series of repeat control halothane contracture tests ($n = 9$) indicated little variability between specimens from the same patient (two-tailed paired *t* test: mean difference 0.04 g, 95% CI = −0.209 g to 0.120 g; $P = 0.584$).

These results suggest that amiloride affects contracture development of MH muscle in response to halothane, providing further evidence of a role for the sarcolemma in the pathophysiology of an MH response. It is likely that amiloride influences sarcolemmal calcium flux by more than one mechanism.

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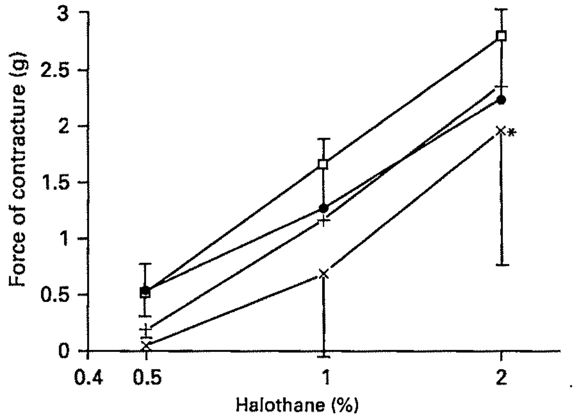

FIG. 6. Mean (95% confidence intervals) contracture responses to incremental additions of 0.5, 1 and 2% halothane in the presence of amiloride 0.5 mmol litre^{-1} (+), 1 mmol litre^{-1} (×) or 2 mmol litre^{-1} (□), and in the absence of amiloride (● = control). $^{*}P < 0.0192$.

ACUTE EFFECT AND RECOVERY OF PRIMARY AFFERENT NERVE FIBRES AFTER GRADED RADIOFREQUENCY LESIONS IN ANAESTHETIZED RATS

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Smith and colleagues [1] showed that exposure of dorsal root ganglia in the dog to a radiofrequency heat pulse of 85 °C, lasting for 2 min, produces permanent destruction of both myelinated and non-myelinated primary afferent neurones.

In clinical use, radiofrequency is used more commonly on peripheral nerves than on dorsal root ganglia. In the present pilot study, we attempted to establish patterns of destruction and regeneration after radiofrequency heat lesions to peripheral nerves.

Both saphenous nerves were exposed under sterile conditions in rats anaesthetized with halothane. One nerve was then treated under visual control with radiofrequency generated heat pulses of either 30 s or 1 min duration. Temperatures ranged from 60 to 90 °C. The contralateral nerve was treated in the same way, except that the radiofrequency generator did not produce any heat. The wounds were then closed and the animals allowed to recover. Between 1 and 2 weeks after the lesion, the animals were killed and both saphenous nerves were prepared for electron microscopy.

Lesions were produced consistently with a temperature of 70 °C lasting 30 s. Both myelinated and non-myelinated fibres were affected. Changes included demyelination and degeneration, depending on the variables used. It was interesting to note that within 2 weeks there was evidence for regeneration in almost all groups of nerve fibres.

In conclusion, even with profound radiofrequency-induced thermal lesions, peripheral nerves may start to regenerate over the whole spectrum of nerve fibres within 2 weeks. This observation can explain the not uncommon return of chronic pain within weeks or months after neurolytic treatment with radiofrequency.

ACKNOWLEDGEMENT

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CONTINUOUS SPINAL ANALGESIA DURING HIGH-RISK LABOUR AND OPERATIVE DELIVERY

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Continuous spinal analgesia has been used in obstetrics for elective Caesarean section [1] and for pain relief during uncomplicated labour and normal delivery [2]. We have investigated its use in a selected group of parturients with complicated labours who are more likely to progress to emergency Caesarean section.

After hospital Ethics Committee approval and informed consent, 12 women were studied. I.v. access was secured and the lumbar subarachnoid space identified in the midline using a 26-gauge Quincke tip spinal needle in 10 patients and a 24-gauge Special Sprotte needle in two patients. A 32-gauge intrathecal catheter was inserted 2–4 cm through the needle and secured. Plain bupivacaine 0.25% was administered in 0.5–1.0-ml increments. Pain was assessed on a 10-cm linear analogue scale before administration of each increment and every 5 min for 15 mins after each increment. Blood pressure was measured non-invasively every 3 min during this time. Fetal heart rate and maternal arterial oxygen saturation were monitored continuously. The degree of motor block was assessed by the Bromage scale [3] when analgesia was adequate.

There were three technical failures in the group. Nine patients had successful analgesia by the continuous spinal technique. The mean incremental dose of 0.25% plain bupivacaine during labour was 0.98 ml (range 0.5–2.0 ml). Analgesia following increments lasted an average of 50.4 min (range 20–110 mins). The mean total dose of 0.25% bupivacaine per patient was 4.8 ml (range 2.0–8.0 ml). Pain scores decreased from an average of 5.46 cm (range 0.9–10.0 cm) before, to 0.71 cm (range 0–4.4 cm) after spinal block.

Three patients required delivery by Caesarean section for failure to progress. A mean additional dose of 0.5% hyperbaric bupivacaine 2.33 ml (range 1.0–4.5 ml) was necessary for Caesarean section. Fetal outcome as assessed by Apgar scoring at 1 and 5 min after delivery was excellent. One patient required an outlet forceps delivery.

Complications included postdural puncture headache (three patients), difficulty threading the catheter beyond the tip of the spinal needle (five patients) and nerve root pain during catheter insertion (three patients).

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DURATION OF ACTION OF 5% INTRATHECAL PETHIDINE *VS* 0.5% HYPERBARIC BUPIVACAINE FOR HIP SURGERY

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Intrathecal pethidine has been used successfully as the sole agent for abdomen and lower limb surgery but with variations in the duration of action of postoperative analgesia [1, 2]. We determined the duration of action of intrathecal pethidine using a pethidine patient controlled analgesia system (PCA) to measure pethidine consumption in the first 24 h after hip surgery.

Written informed consent was obtained from patients (ASA I–III) undergoing hip surgery excluding those patients with conditions which contraindicated the use of an intrathecal technique or who were unable to use a PCA. Patients were premedicated with an oral dose of temazepam 10 mg, 1 h before operation. In the anaesthetic room non-invasive arterial pressure and oxygen saturation monitoring were established and patients were preloaded with Hartmann's solution 500 ml. Patients were allocated randomly to receive pethidine 1 mg kg^{-1} or an equivalent volume of 0.5% hyperbaric bupivacaine intrathecally. The observer was blind to the drug administered and sedation was achieved with a propofol infusion at the patient's request. After operation a PCA was set up using a bolus dose of pethidine 5 mg with a 5-min lockout period and the patient admitted to a high dependency unit. Pethidine consumption and pain scores were recorded at 1, 2, 3, 4, 6, 8, 12 and 24 h. Oxygen saturation values less than 90% were treated with oxygen and side effects were recorded. Statistical analysis was by Mann-Whitney U test, Student's t test and Fishers exact test as appropriate.

Data from the first nine patients in each group are presented. There were no differences between the groups in age, weight, sex, ASA grades or duration of operation. Seven patients in each group requested sedation. Lower pain scores ($P < 0.05$) and a lower pethidine consumption was observed in the pethidine group ($P < 0.05$) at 3 h. There were no other significant differences in pain scores or pethidine consumption at any other time, although the pethidine groups used less pethidine at all time points (mean consumption at 24 h 183 (39) cf. 234 (33) mg). There was no difference in return of motor function and there were no neurological or respiratory problems in either group.

We conclude that intrathecal pethidine may be used as the sole agent for major lower limb surgery but profound analgesia lasts for 3–4 h after intrathecal injection compared with 2–3 h for an equivalent volume of bupivacaine but with reduced requirements for PCA pethidine.

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METHOXAMINE AND PERIPHERAL BLOOD FLOW DURING SUBARACHNOID ANAESTHESIA

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Subarachnoid anaesthesia causes vasodilation and increased blood flow in the lower limbs and is accompanied by reverse changes in the upper limbs [1, 2]. The aim of this study was to examine the effects of methoxamine on subarachnoid anaesthesia associated changes in upper and lower circulations.

After Ethics Committee approval and informed consent, 10 healthy patients undergoing elective surgery were included in the study. Patients were not preloaded with i.v. fluids. Subarachnoid anaesthesia was established with 0.5% hyperbaric bupivacaine 3 ml at the L3–4 interspace. A bolus dose of methoxamine 2 mg was administered i.v. when mean arterial blood pressure (MAP) decreased by 15% below the preinduction value. Limb blood flow was measured using venous occlusion plethysmography with a mercury-in-silastic strain gauge. Measurements were obtained simultaneously from the right arm and leg at 1-min intervals starting 10 min before subarachnoid anaesthesia and continuing until 5 min after the administration of the bolus dose of methoxamine. Calf blood flow (CBF), forearm blood flow (FBF ml 100 ml^{-1} min^{-1}), heart rate (HR) and MAP (mm Hg) were recorded. Calf and forearm vascular resistance (CVR, FVR) were derived and expressed as arbitrary R units. Patients acted as their own controls. Data were analysed using repeated measures analysis of variance and Student's t test. Statistical significance was assumed where $P < 0.05$.

After spinal anaesthesia, HR, CBF and FVR increased significantly while MAP, CVR and FBF decreased significantly. Two minutes after a bolus dose of methoxamine when changes were maximal, there was a significant decrease in HR and FVR and a significant increase in MAP, FBF and CVR (table VII).

Methoxamine reverses the changes in limb flow produced by subarachnoid anaesthesia. Methoxamine produces opposing effects in the upper and lower limbs. These changes are transient except for the effect on HR.

TABLE VII. *Mean* (SEM) *haemodynamic variables before* (*Baseline*) *and 2 min after administration of methoxamine.* **$P < 0.01$; ***$P < 0.001$ *compared with baseline values*

	Baseline	After methoxamine
HR	72 (4)	57 (4)***
MAP	84 (4)	95 (4)**
CBF	2.6 (0.4)	2.1 (0.5)
CVR	38 (5)	56 (7)**
FBF	1.8 (0.3)	2.5 (0.4)**
FVR	62 (8)	46 (5)**

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USE OF A TOTAL I.V. ANAESTHETIC TECHNIQUE USING GUAIPHENESIN, KETAMINE AND DETOMIDINE IN HORSES: ENDOCRINE CHANGES AND DETOMIDINE CONCENTRATIONS

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In horses, anaesthesia is maintained generally with volatile agents; however, these drugs may cause substantial cardiovascular and respiratory depression [1]. In addition, Taylor has reported activation of adrenocortical responses by halothane anaesthesia (in the absence of surgery) in ponies [2]. There have been reports of the use of total i.v. anaesthesia (TIVA) as an alternative anaesthetic regimen to avoid these problems [3], but there have been few studies describing the efficacy, endocrine changes and associated drug concentrations during anaesthesia.

We studied eight trained pony geldings (aged 2–6 yr, weight 218–340 kg) whose carotid loops had been raised previously. Arterial blood pressure and blood gases were measured via a carotid arterial cannula. Anaesthetic agents were administered via a second cannula in the jugular vein.

After premedication with acepromazine 0.03 mg kg^{-1} i.m., 1 h before the study, hypnosis was induced with the i.v. combination of detomidine 20 µg kg^{-1} followed 5 min later by ketamine 2 mg kg^{-1}. The trachea was intubated after achieving lateral recumbency, and the animals breathed spontaneously oxygen-enriched air. Anaesthesia was maintained with an infusion of guaiphenesin, ketamine and detomidine 100 mg ml^{-1}, 2 mg ml^{-1}, 20 µg ml^{-1}, respectively, administered by a volumetric pump according to the standard regimen of 1.6 ml kg^{-1} h^{-1} for 1 h, 1.3 ml kg^{-1} h^{-1} for 30 min and 1.0 ml kg^{-1} h^{-1} for 30 min. At the end of 2 h, the infusion was stopped and the ponies allowed to recover.

Venous blood samples were obtained for plasma concentrations of cortisol, ACTH and detomidine after premedication (control), after tracheal intubation ($t = 0$), at 20, 40, 60, 90 and 120 min during infusion, at the time of first movement and at time of standing. Cortisol and ACTH were measured by RIA, and detomidine by ELISA (Horseracing Forensic Labs., Newmarket).

Anaesthesia was uneventful in all ponies. Intraoperative blood pressure and blood gases were close to the normal range for conscious horses (range of mean values: mean arterial pressure 101–148 mm Hg, Pa_{O_2} 15.7–18.1 kPa, Pa_{CO_2} 6.5–7.3 kPa, pH 7.36–7.40). Recovery to standing took between 25 and 123 min.

Plasma concentrations of ACTH, cortisol and detomidine are shown in figure 7. Unlike the increases seen with halothane [2], TIVA resulted in no change in ACTH concentrations; the plasma concentrations of cortisol decreased during the infusion. Both hormones increased after the end of anaesthesia. Plasma concentrations of detomidine showed wide variability at the first time point (intubation) reflecting differences in time of sampling. Thereafter, there was less variability; individual concentrations between 20 and 120 min ranged from 13.8 to 238 ng ml^{-1}, the mean concentrations increasing from 58 to 130 ng ml^{-1}. At the time of first movement and standing, concentrations of detomidine were not significantly different from values at 120 min, and in fact increased in some animals. The significance of the latter finding is not certain.

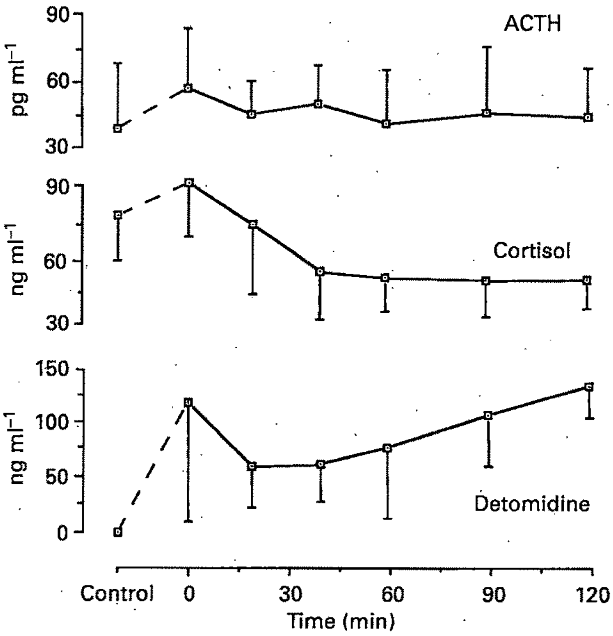

FIG. 7. Mean (SD) plasma concentration of ACTH, cortisol and detomidine after tracheal intubation (Control) and during TIVA infusion of guaiphenesin, ketamine and detomidine.

These preliminary observations confirm the efficacy of the technique, but further study is needed to define more clearly the infusion kinetics of detomidine. There is a suggestion that infusions of detomidine, an alpha-2 agonist similar to clonidine, may suppress the activity of the pituitary-adrenocortical axis.

ACKNOWLEDGEMENTS

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EFFECT OF VOLATILE ANAESTHETIC AGENTS ON CHOLINE ACETYLTRANSFERASE ACTIVITY *IN VITRO*

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Investigations in animals have shown that the release of acetylcholine in the cerebral cortex is related to convulsions and to electroencephalogram (EEG) seizure-like activity. Administration of enflurane may be associated with tonic–clonic muscle twitching and EEG abnormalities in man.

Changes in the rate of synthesis or release of acetylcholine from the neurone may account for these effects. Choline acetyltransferase catalyses the synthesis of acetylcholine from the precursors choline and acetyl coenzyme A. We studied the effects of the halogenated anaesthetic agents on the activity of choline acetyltransferase in a synaptosome preparation from the rat brain cortex.

Rat brain synaptosomes were prepared using a modification of the technique described by Gray and Whittaker [1]. Halothane, enflurane and isoflurane (3 MAC (rat)) were delivered in air to the synaptosome preparation using calibrated vaporizers. Choline acetyltransferase activity was determined by measurement of the incorporation of [^{3}H]-acetyl coenzyme A into acetylcholine [2].

Maximum rate of reaction (*V*max) and Michaelis constant (K_m) were calculated and results compared using analysis of variance and Student's paired t test as appropriate.

Mean (SEM) *V*max and K_m values of the 12 preparations in each group are shown in table VIII. Enflurane reduced the K_m value significantly ($P = 0.012$).

These *in vitro* data suggest that enflurane may facilitate the synthesis of acetylcholine *in vivo* which would be consistent with enflurane-induced epileptiform patterns on the EEG. Halothane and isoflurane showed no effect on choline acetyltransferase activity and this concurs with the lack of effect of halothane on this system reported previously [3]. We are investigating the effects of these agents on synaptic release and re-uptake mechanisms.

TABLE VIII. *Mean (SEM) Vmax and K_m values in 12 rat brain synaptosome preparations after the addition of halothane, enflurane and isoflurane*

	*V*max ($\text{nmol mg}^{-1}\ \text{min}^{-1}$)		K_m (µmol)	
	Air	Agent	Air	Agent
Halothane	0.84 (0.11)	0.80 (0.06)	0.26 (0.04)	0.23 (0.04)
Enflurane	0.80 (0.04)	0.84 (0.05)	0.24 (0.03)	0.15 (0.02)
Isoflurane	0.80 (0.04)	0.78 (0.08)	0.24 (0.03)	0.24 (0.04)

ACKNOWLEDGEMENT

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NECK FLEXION AND COMMON AIRWAY MEASUREMENTS

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Recent attention has focused on factors affecting upper airway patency and the effects of tongue size in difficult intubation. Earlier work has suggested that neck flexion alters "airway space" [1]. Because of our own investigations of the influence of head and neck posture on indices affecting ease of intubation, we were interested on the effect of neck flexion on simple airway measurements. Preliminary studies suggested changes do occur. Neck flexion to 30° was chosen for further study because of our intubation investigations.

Forty-eight healthy volunteers, ages 21–45 yr (mean 27.5, SD 5.2 yr) with no history to indicate active respiratory or airway problems were studied. Each subject performed three sets of tests, with each test performed in both a neutral and neck flexed position. The tests performed were; peak nasal inspiratory flow rate (PnIFR) using a Youlten PnIFR meter; peak oral expiratory flow rate (PEFR) using a Wright's peak flow meter; and FEV_1 and FEV using a Vitalograph. Measurements were performed with the subject sitting erect on a stool. The neutral and 30° flexion positions were confirmed using "angle finder" [2]. Subject movement was minimized by the observer's hand resting against the forehead during the testing. For each test and position, three satisfactory measurements were recorded and the best of these used. Subjects were block randomized (by selecting cards) into four study groups as shown in table IX.

Nasal measurements were performed first in all subjects to prevent effects from forced expiratory manoeuvres. There were five, six, seven and seven males in groups 1, 2, 3 and 4, respectively. Change was defined as a 20% decrease in measurement in the flexion position relative to that in the neutral position.

All subjects were within 20% of their ideal weight for height and build and produced measurements in the neutral position consistent with predicted values in 48/48 patients for FEV_1 and 45/48 for PEFR. Change, as defined above, was observed in 2/48 patients for FEV_1 and 1/48 for PEFR. However, 24/48 patients showed changes in PnIFR; 15/24 of these occurred when the neutral position was tested first and the remaining 9/24 when flexion was tested first ($P > 0.05$).

PnIFR has been shown to be particularly influenced by neck flexion and this should be considered when performing this routine investigation.

TABLE IX. *Order of positioning for tests*

Test sequence	Neutral then flexion	Flexion then neutral
1. PnIFR 2. FEV 3. PEFR	Group 1	Group 3
1. PnIFR 2. PEFR 3. FEV	Group 2	Group 4

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POSTER PRESENTATIONS

A UNIVERSAL COMPUTER INTERFACE

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Most of the equipment used for monitoring provides some kind of data output, and many syringe drivers and ventilators have control inputs. Unfortunately, there is no standard for these connections. Even the RS232 digital connection is only an electrical standard; there is an infinite number of protocols.

This equipment was designed to provide an easy to use solution to the technical problems of interfacing several different items of equipment to a computer simultaneously. It has been designed for clinical reasearch workers with little knowledge of computer hardware or software. The unit is bi-directional and can be used for data collection or, with appropriate software, for closed loop control studies.

The unit is based on an Intel 80196KB microcontroller and provides eight bi-directional RS232 ports, eight analogue input channels and four analogue output channels. Each input/output is entirely under software control, including control of baud rate, parity, data and stop bits, DTE/DCE connections for the digital ports and gain and offset control for the analogue ports. This wide ranging input/output specification should allow interfacing to almost any item of equipment. The whole communicates with the host computer using a single RS232 port and a standard string format. Although the prototype system uses an IBM AT computer as host, any machine that has an RS232 serial port and for which a C compiler is available could be used.

The individual ports will be set up from the host computer using a simple menu. Set-up data for commonly used equipment will be pre-stored on disc. Data can be sampled from the monitoring equipment as often as required and will be transferred automatically to the host for storage in a database program. Some pre-processing of the incoming data will be possible to reduce the quantity of redundant data stored.

The electronic design of the interface is now complete and a prototype has been constructed. The software is being written in C and most of the required functions have been written and tested.

USING BONDS GRAPHS TO REPRESENT PHARMACO-PHYSIOLOGICAL MODELS

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Pharmaco-physiological models are used frequently in research and teaching. They range in type from quantitative physiological models represented by equations, to compartmental models of blood concentration and qualitative models represented as analogues (e.g. electric circuit) and to text. The ability to understand, use, develop and disseminate a model can be hindered by the model representation, for example graphics, text, mathematical equations or computer code. Our objective is to introduce the use of Bond Graphs (BG) for model construction and analysis in anaesthesia.

BG representation is a single graphical scheme [1] which can illustrate, by a common symbol set, models as diverse as those representing electrical circuits, mechanical systems and money flow. BG are based upon physical principles, for example conservation of energy.

Because the representation is standardized, the whole modelling process can be performed using a computer to manipulate images. This involves drawing the BG and inserting constant values. Equations may then be derived automatically from the BG as drawn and used to perform analysis, simulation and design. Current BG software (developed in Glasgow) runs on Sun workstations but further versions are expected for other computers.

One powerful feature of BG is that the notation allows models to be combined, for example the pharmacokinetic model for a beta-blocker can be combined with the pharmacodynamic model, and these linked to a subject's exercise capability.

Examples of the Mapleson type models have been demonstrated [2] with the equivalent BG and their model simulations. Additional examples show standard compartmental models with their BG and simulated blood concentration data following step inputs of a drug.

We believe that BG are an important analytical tool in pharmacology and that the use of the technique merits further investigation.

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CHANGING ANAESTHETIC PRACTICE CAN AFFECT THE EVALUATION OF POSTOPERATIVE NAUSEA AND VOMITING

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Investigating postoperative sickness using both subjective (nausea) and objective (vomiting) variables is fraught with problems. Variable factors which should be controlled include the sex of the patient, premedication and anaesthesia, and the nature and duration of operation, while the individual tendency can only be overcome by studying large numbers of comparable patients. A satisfactory technique, developed by the Belfast Department, using a standard anaesthetic and variable premedication administered to women undergoing minor gynaecological operations has been used in more than 2000 patients over a period of 10–15 yr [1].

A comparison of the relative efficacy of various methods of stimulation of the P6 acupuncture point has been reported previously [2]. Premedication consisted of nalbuphine 10 mg and anaesthesia was induced with methohexitone and nitrous oxide in oxygen. The incidence of sickness in the control series, although high, was acceptable with the drugs available at that time, and was reduced by the concomitant administration of an effective antiemetic. Five years later we evaluated a simple machine for self-administration of transcutaneous electrical stimulation of P6 in the same patient population, but in the interim a day-case unit had been opened and methohexitone was replaced with propofol. The influence of these changes on the incidence of sickness is shown in table X.

Propofol was an unsuitable agent for antiemetic studies. Even when a "compromise" technique of alfentanil and methohexitone was used the incidence of sickness was still too low, and recovery was too slow for routine use.

These observations show that a standard study method may have a limited period of use. Clearly it would be unethical to revert to an outdated technique for the purposes of clinical research.

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TABLE X. *Postoperative sickness (vomiting including retching and vomiting with nausea, and nausea alone) in the first 4–6 h after operation, related to anaesthetic technique*

	Anaesthetic technique	Vomiting	Nausea
1985–1986	Methohexitone and nalbuphine ($n = 56$)	14	24
1990–1991	Propofol ($n = 26$)	0	4
	Methohexitone and alfentanil ($n = 21$)	6	1

TABLE XI. *Individual and median time to 50% emptying of a liquid meal (T_{50}) in subjects receiving no alcohol (Control) and after consumption of 3 or 6 units of alcohol.* **$P < 0.018$ *compared with control*

	T_{50} (min)		
Subject	Control	Alcohol (3 units)	Alcohol (6 units)
1	27	41	27
2	22	27	50
3	23	24	63
4	36	16	45
5	13	10	19
6	17	24	36
7	29	47	90
8	27	49	45
Median	25.0	25.5	47.5**

EFFECT OF ALCOHOL ON GASTRIC EMPTYING

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Regurgitation of gastric contents is of particular concern during anaesthesia for emergency surgery which is often associated with recent alcohol ingestion. The effect of alcohol on gastric emptying is unclear [1, 2]. The purpose of this study was to measure the effect of alcohol on gastric emptying of a liquid meal.

Gastric emptying was measured by applied potential tomography. This technique measures changes in resistivity of gastric contents as the stomach empties [3].

Eight healthy, non-smoking male volunteers (aged 27–42 yr) were allocated randomly to receive no alcohol, 3 units of alcohol (whisky 75 ml in water 25 ml) or 6 units of alcohol (whisky 150 ml in water 50 ml) at least 1 week apart. On each occasion, the subject was fasted overnight and cimetidine 800 mg was administered orally (histamine H_2 receptor block is required as gastric acid secretion may affect resistivity measurements). One hour later, alcohol was ingested over 20 min; 40 min later, beef consommé soup (Campbell's) 500 ml was ingested.

Resistivity measurements were taken over 90 min and time to 50% emptying (T_{50}) was calculated. Data were analysed by Friedman's analysis of variance and Wilcoxon test for paired data.

Individual and median T_{50} values are shown in table XI.

We have shown that 6 units of whisky delayed significantly gastric emptying of a liquid meal.

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DETERMINATION OF CARDIAC OUTPUT IN THE STANDING HORSE BY THERMODILUTION AND DOPPLER ECHOCARDIOGRAPHY

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Doppler echocardiography is a non-invasive technique which has been used to estimate cardiac output. Cardiac output estimations obtained by this method have been compared to measurements made by thermodilution in humans [1] and in dogs. In order to assess the technique in standing horses, we measured the cardiac output using simultaneously transthoracic Doppler echocardiography and thermodilution. Echocardiographic examinations were performed using a Vingmed CFM 7 00 ultrasound machine. Thermodilution cardiac output calculations were performed using a Cardiomax II cardiac output computer (Columbus Instruments, Ohio).

Spectral velocity waveforms were recorded from the pulmonary artery and the aorta. The mean of five successive velocity time integrals, synchronous with injectate administration, were used for the calculation of cardiac output. Measurements of vessel diameter used for calculation of cross-sectional area were made as follows: aorta: diameter of vessel including leading edge, inner diameter of vessel, aortic valve diameter including leaflet, inner aortic valve diameter, sinus of Valsalva, diameter from an M-mode image; pulmonary artery: inner diameter of vessel, diameter including one vessel wall, diameter including both walls.

Spectral enhancement of pulmonary artery velocity profiles occurred after introduction of a dextrose solution so that velocity time integral measurements were made from five profiles immediately before injection of the cold contrast injection and from five profiles at the time of injection. The two measurement techniques were compared whilst the horses were standing quietly, during the i.v. infusion of dopamine and dobutamine, and after the horses had been sedated using the alpha-2 agonist detomidine.

The best correlation between estimations of cardiac output were observed using the aortic velocity profiles when the diameter of the sinus of Valsalva was used to calculate vessel area ($r = 0.88$). The poorest correlation was derived from the inner edge of the aorta when $r = 0.85$. The best estimates of cardiac output from the pulmonary artery flow profiles were obtained when the vessel diameter was measured to include the vessel wall and when the velocity time integral was computed during the injection of cold contrast ($r = 0.80$).

ACKNOWLEDGEMENT

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A QUANTITATIVE *IN VITRO* ANIMAL MODEL OF SUXAMETHONIUM- AND HALOTHANE-INDUCED MUSCLE DAMAGE

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We tested the feasability of adapting an *in vitro* animal model of calcium-induced muscle damage described previously [1] to provide quantitative measures of the muscle damage caused by halothane (clinically evident in those susceptible to malignant hyperthermia) and by suxamethonium (as evidenced by suxamethonium myalgia and malignant hyperthermia).

Soleus and extensor digitorum longus (EDL) muscles were carefully dissected from rats killed by cervical dislocation. The muscles were pinned through their tendons to plastic frames and placed in individual sealed containers with Krebs solution 10 ml at 37 °C and aerated continuously with 5% carbon dioxide in oxygen. After each of four 30-min periods the incubating medium was drained completely but retained for analysis of creatine kinase (CK) concentrations (NADH-linked enzyme assay) and replaced by fresh Krebs solution. The second aliquot of Krebs solution contained either halothane 0.44 mmol litre^{-1} or suxamethonium 20 μmol litre^{-1} alone, or halothane 0.44 mmol litre^{-1} and suxamethonium 20 μmol litre^{-1}, or no drug (control).

CK efflux for the 2nd, 3rd and 4th 30-min periods were expressed as a ratio of the initial CK efflux to allow for variation between muscles in background rate of CK efflux. The distribution of results obtained was skewed and therefore the data were normalized using logarithms [2]. The logged data were subjected to a one-way ANOVA and 95% confidence intervals for differences between groups obtained using subsequent Scheffé tests.

Table XII shows the comparisons of the various groups of treatments in the two muscle types. The second group of each pair produced the greater CK efflux.

TABLE XII. *Comparisons of the various groups of treatment on the soleus (Sol) and extensor digitorum longus (EDL) muscles after exposure to halothane (HAL), suxamethonium (SUX), halothane and suxamethonium (S+H) or no drug (CON). The antilogged 95% confidence interval (I) and the differences between the geometric means of the CK efflux during the 2nd, 3rd and 4th periods (D2, D3 and D4) are shown. (Number of preparations in each group.)* $^{\star}P < 0.05$

	I	D2	D3	D4
$\mathrm{Sol_{CON}}$ (10) *vs* $\mathrm{sol_{HAL}}$ (9)	3.64	4.61*	1.82	1.60
$\mathrm{Sol_{CON}}$ (10) *vs* $\mathrm{sol_{SUX}}$ (13)	3.27	1.60	4.29*	6.71*
$\mathrm{Sol_{HAL}}$ (9) *vs* $\mathrm{sol_{SUX}}$ (13)	3.39	−3.01	2.45	5.11*
$\mathrm{Sol_{SUX}}$ (13) *vs* $\mathrm{sol_{S+H}}$ (4)	6.08	6.45*	1.97	0.70
$\mathrm{Sol_{HAL}}$ (9) *vs* $\mathrm{sol_{S+H}}$ (4)	6.55	3.44	0.48	5.81
$\mathrm{EDL_{CON}}$ (9) *vs* $\mathrm{EDL_{HAL}}$ (9)	3.78	34.56*	12.54*	5.00*
$\mathrm{EDL_{CON}}$ (9) *vs* $\mathrm{EDL_{SUX}}$ (10)	3.64	1.31	5.00*	6.22*
$\mathrm{EDL_{SUX}}$ (10) *vs* $\mathrm{EDL_{HAL}}$ (9)	3.64	33.25*	7.54*	1.21
$\mathrm{Sol_{CON}}$ (10) *vs* $\mathrm{EDL_{CON}}$ (9)	3.64	0.854	0.863	2.40
$\mathrm{Sol_{SUX}}$ (13) *vs* $\mathrm{EDL_{SUX}}$ (10)	3.27	0.564	1.59	1.90
$\mathrm{Sol_{HAL}}$ (9) *vs* $\mathrm{EDL_{HAL}}$ (9)	3.78	30.80*	11.59*	5.80*

An *in vitro* method of quantifying skeletal muscle damage after exposure to halothane and suxamethonium has been demonstrated. The effect of halothane occurred early and was greater in type II fibres (EDL). The effect of suxamethonium appeared later and was similar in type I and type II fibres.

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EMERGENCY ANAESTHETIC SERVICE AT THREE HOSPITALS: I METHODS AND RESULTS

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A 6-week audit of emergency anaesthetic services was carried out at the Royal London Trust (RLT), Northampton General Hospital (NGH), and Royal Liverpool Children's Hospital, Alder Hey (AH). The aim of the study was to analyse emergency anaesthetic workload and compare results with earlier surveys [1, 2].

The following data were collected for all emergency anaesthetic requests: date of event; hospital; anaesthetists on-call; patient hospital number; date and time of patient admission; date and time of decision and initial request for anaesthetic service; emergency category as stated by requesting doctor and assessed by anaesthetist; grade of anaesthetist suitable; agreed and actual start time committed to patient; time finished and available for work; type of work; location of anaesthetist at time of initial request for service; and comments. The ICU work was treated separately and recorded every 15 min on a diary form.

The RLT, NGH and AH recorded 594, 459 and 366 emergency events, respectively (theatre cases, arrest/trauma calls, patient transfer, etc.), other than those recorded by the anaesthetists in the ICU. The average number of events per day was 13.9, 10.9, 8.3, respectively, with an average duration of 87 min at RLT, 58 min at NGH and 76 min at AH. The number of emergency events by day of the week was higher on Fridays at RLT and AH, and more evenly distributed throughout the week at NGH. At RLT 55% of emergency events were between the hours of 17:00 and 02:00 (23% 17:00–20:00, 21% 20:00–23:00 and 11% 23:00–02:00). At NGH 46% of emergency events occurred between 17:00 and 02:00 (15% 17:00–20:00, 22% 20:00–23:00 and 9% 23:00–02:00). At AH 57% of emergency events were between 17:00 and 02:00 (19% 17:00–20:00, 23% 20:00–23:00 and 15% 23:00–02:00). All events were assessed for priority by the requesting doctor and the responding anaesthetist (1 = immediate to 5 = elective out of hours). Emergency category 3 (urgent: 1–2 h) accounted for the largest percentage (52.5%) of the total emergency workload (RLT 40%; NGH 50%; AH 69%). At NGH there was good agreement between the requesting doctor and the anaesthetist for all categories; at the other two hospitals there was agreement for categories 1, 2 and 5, with 4–10% of category 3 cases revised to category 4. At all hospitals the most junior on-call staff responded to a high proportion of the emergency events, with 43% of all cases at RLT treated by a registrar and 43% by a senior house officer. At NGH, 50% of all cases were treated by a senior house officer; at AH 58% of all cases were treated by a registrar (the most junior member of the department). The responding anaesthetists were asked to comment on the grade suitable for each case. Overall, the majority of cases were managed either by the most suitable or by a more than suitable anaesthetist, but for each hospital there was a proportion of cases which were thought to have been treated by anaesthetists who might have benefited from more senior assistance (RLT 13%; NGH 9%; AH 12%).

Between 46% and 57% of all emergency events at the three hospitals occurred between 17:00 and 02:00. The most junior anaesthetists responded initially to the calls. A significant number of events were managed by anaesthetists who were felt subjectively to be unsuitable.

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EMERGENCY ANAESTHETIC SERVICE AT THREE HOSPITALS. II OBSTETRIC ANAESTHETIC SERVICES

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Using similar methods described previously [1,2] a repeat 6-week audit of emergency anaesthetic services was carried out at the Royal London Trust (RLT), Northampton General Hospital (NGH) and Royal Liverpool Children's Hospital, Alder Hey (AH). An apparent increase in the demand for obstetric anaesthesia and pain relief prompted a more detailed examination of obstetric workload at RLT and NGH

Of the total emergency workload, almost half of the cases (46%) at NGH were obstetric (e.g. extradural analgesia for labour, emergency Caesarean section), but the proportion at RLT was considerably less (22%).

At NGH there were 4242 deliveries in 1990 (4170 in 1978) but with a doubling in the rate of emergency Caesarean section from 4.9% to 10% and a similar increase in the rate of extradural analgesia from 12.9% to 25%. At RLT there were 3413 deliveries in 1990, 9.6% of which were emergency Caesarean sections and 12.9% extradural analgesia for labour.

At both sites, anaesthetic on-call cover for the obstetric department was provided by a registrar grade anaesthetist throughout the 24 h. At NGH the registrar grade spent 88% of their on-call working time in obstetric anaesthesia, a much greater proportion than at RLT (35%).

The demand for obstetric services was spread evenly throughout the 24 h, whereas there were few calls for non-obstetric work between 24:00 and 08:00. At NGH, 75% of all calls between 24:00 and 08:00 were for obstetric work, and this increased to 94% for the period between 03:00 and 08:00. (Comparable figures for RLT were 42% (24:00–08:00) and 63% (03:00–08:00.) During the 6-week study the registrar covering the obstetric on-call was undisturbed by calls from the labour ward between 24:00 and 08:00 in only 1 night in 4 at NGH, compared with 1 night in 2 at RLT.

The survey highlights the heavy workload an active obstetric anaesthetic service generates and the large proportion of registrar on-call time spent covering obstetric anaesthesia in a typical district general hospital. This may have implications for the training of registrars and emphasizes the importance of time off after nights on call.

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EMERGENCY ANAESTHETIC SERVICE AT THREE HOSPITALS. III OUT OF HOURS WORKLOAD

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CORRESPONDENCE

OVERDOSE OF OPIOID FROM PATIENT CONTROLLED ANALGESIA PUMPS

Sir,—In our hospital there have been two episodes, at an interval of 1 year, of Patient Controlled Analgesia (PCA) pumps delivering the entire contents of a 60-ml syringe of opioid as a bolus (diamorphine 60 mg over approximately 40 min). Both patients were receiving PCA for control of postoperative pain and were being managed on general surgical wards according to our standard policy [1]. The nurses were alerted by the "Syringe Empty" alarm of the pumps. Both patients suffered severe respiratory depression, but were successfully resuscitated. They made satisfactory recoveries and suffered no ill effects.

Both the episodes were reported to the Department of Health, who inspected the pumps. The pump manufacturers, Graseby Medical, Watford, England, traced both faults to corruption of the pumps' software by either mains electricity fluctuations or static electricity discharges from the patients' beds. Corruption of the software from both these sources had often been observed in our hospital. However, the pumps had previously always "failed-safe". After both incidents, Graseby carried out modifications to all their pumps.

PCA has been widely used for many years. There are only two other such episodes described in the literature. The first related to syphoning from a cracked syringe and the second is of uncertain aetiology [2, 3]. A third such incident occurred in Tasmania in 1990 [personal communication]. Nearly 5000 patients have used PCA from 31 PCA pumps in this hospital, reflecting some 200000 h use. However, this must be set against the huge worldwide usage of PCA and the Graseby pumps.

We are continuing to review our management of PCA as part of a wider review of patients requiring High Dependency Care on general wards. We have continued to use PCA as our main postoperative analgesic technique for severe pain. We urge manufacturers to continue to improve the fail-safe mechanisms in their equipment.

Full details of both incidents will be published as a Case Report.

W. Notcutt
Great Yarmouth

1. Notcutt WG, Morgan RJM. Introducing patient controlled analgesia for postoperative pain control into a District General Hospital. *Anaesthesia* 1990; **45**: 401–406.
2. Thomas DW, Owen H. Patient controlled analgesia—the need for caution. *Anaesthesia* 1988; **43**: 770–772.
3. Grey TC, Sweeney ES. Patient controlled analgesia. *Journal of the American Medical Association* 1988; **259**: 2240.

THE EPIC STUDY

Sir,—On behalf of the EPIC Study Advisory Committee, I would like to draw the attention of all specialists in intensive care to the European Prevalence of Infection in Intensive Care (EPIC) Study and urge all intensive care units to participate in this study on April 29, 1992.

The EPIC Study is the largest of its kind to look at the problem of nosocomial infection in intensive care units from a European perspective and will take place in 17 countries throughout Western Europe. This will be the first time that the prevalence of infection in the ICU has been related to the severity of illness of the patient on admission, in combination with an assessment of the adequacy of treatment in patient survival. The results published will be a major contribution to the literature on the subject, and should provide many new insights into the course of infection in susceptible patients, and the likely outcome.

This is a one-day prevalence study which has been chosen as the simplest, most cost effective and least disruptive study method. The guidelines developed by the Centers for Disease Control for the diagnosis of nosocomial infection will be used. These definitions can be used for prevalence surveys and outbreak investigations in addition to routine surveillance of nosocomial infections [1]. Using the same definitions and similar surveillance methods will enable comparisons to be made with NNIS data.

It is hoped that the European database generated by the EPIC Study will have a significant role in the assessment of future infection control procedures. Nosocomial infections in the intensive care unit have a major cost in terms of patient morbidity and mortality and also in economic terms. In 1989, the average associated cost for a nosocomial infection was estimated at US$ 1800 [2]. More recently in Switzerland, hospital infection has been estimated to cost in the range of SF 100–300 million per year [3].

The EPIC Study is being planned and directed by the EPIC Study Advisory Committee, made up of 17 members from Western Europe. The study is funded by Roussel Uclaf as part of their commitment to the control and management of hospital infection.

It is particularly important that as many units as possible contribute data, so that the results are representative. For further information, please write to EPIC Study Co-ordinator, Medical Action Communications Ltd, Action International House, Crabtree Office Village, Eversley Way, Thorpe, Egham, Surrey TW20 8RY (U.K.); Fax: 0784 431323. Units which have already registered will receive information automatically.

D. Bihari
EPIC Study Advisory Committee

1. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections. *American Journal of Infection Control* 1988; **16**: 128–140.
2. Daschner F. Cost-effectiveness in hospital infection control—lessons for the 1990s. *Journal of Hospital Infection* 1989; **13**: 325–336.
3. Geroulanos S, Attinger B. Nosocomial infections, risks and consequences. *Schweizerische Rundschau für Medizin Praxis* 1991; **80**: 291–296.

COMBINED SPINAL–EXTRADURAL ANAESTHESIA

Sir,—Having interests similar to those of Dr Carrie, I was interested to read his review [1] and the subsequent associated correspondence [2, 3]. I should like to respond to Dr Carrie's final paragraph, in which he invited further revelations of the combined spinal and extradural (CSE) technique.

Prompted by Brownridge [4], I believed that a low spinal combined with a higher extradural block would be efficacious during elective Caesarean section, but it seemed more logical to use the Tuohy needle as the introducer. Difficulty was experienced in obtaining long enough spinal needles but eventually, with a Steriseal 110-mm length 25-gauge metal spinal needle, the CSE was underway; the earliest anaesthetic record I can find is dated November 2, 1981.

I embarked on a formal study in 1982–83, accumulating approximately 80 cases and presented the work at an open meeting of the Munro Kerr Society (for the Study of Reproductive Biology) in association with the Sesquicentennial anniversary of the Glasgow Royal Maternity Hospital in 1984. It is pertinent to state that, in our hospital at least, the advent of spinal anaesthesia as first choice for elective Caesarean section stems from this introduction of CSE and, from 1983 onwards, this form of block superseded the extradural variety.

I now use CSE for deliveries for which the duration of operation may be difficult to judge, in which assessment of spinal dosage may be problematic because of abdominal size (for example prematurity) and in multiple pregnancy.

I commend Dr Carrie for his work and writings on this topic and thank him for this chance to contribute towards it.

D. J. M. Ferguson
Glasgow

1. Carrie LES. Extradural, spinal or combined block for obstetric surgical anaesthesia? *British Journal of Anaesthesia* 1990; **65**: 225–233.

2. Eldor J. First use of combined spinal–extradural anaesthesia. *British Journal of Anaesthesia* 1991; **67**: 666.
3. Carrie LES. First use of combined spinal–extradural anaesthesia. *British Journal of Anaesthesia* 1991; **67**: 667.
4. Brownridge P. Epidural and subarachnoid analgesia for elective Caesarian section. *Anaesthesia* 1981; **36**: 70.

MASSETER SPASM AFTER SUXAMETHONIUM

Sir,—On reading Dr Saddler's editorial on masseter spasm, I was surprised to find no mention of relevant studies on muscles of the hand [1]. I was also a little puzzled by this, as recent work from his own department has shown that there is an excellent correlation between the tension changes occurring in the muscles of the hand and those in the jaw [2].

It seems likely that the high incidence of clinically evident masseter spasm which has been reported in some children's hospitals [3, 4] involves a difference in response to suxamethonium between children and adults, together with differences in clinical practice. Studies at our hospital suggest that children require at least 2 mg kg^{-1} of suxamethonium to produce conditions for tracheal intubation comparable to those obtained with a dose of 1 mg kg^{-1} in adults [5, 6]. In addition, the previously recommended dose for children of 1 mg kg^{-1} [7] was shown to produce a very brief period of neuromuscular block in some patients, while producing the maximum initial increase in muscle tone. Taken together, these results indicate that use of suxamethonium 1 mg kg^{-1} could give rise to inadequate neuromuscular block in some children who would, nevertheless, exhibit maximum muscle spasm. It is not difficult to see how, in the presence of light anaesthesia, such children might be thought to exhibit an abnormal response to suxamethonium.

G. Meakin
Manchester

1. Saddler JM. Jaw stiffness—an ill understood condition. *British Journal of Anaesthesia* 1991; **67**: 515–516.
2. Plumley MH, Bevan JC, Saddler JM, Donati F, Bevan DR. Dose-related effects of succinylcholine on the adductor pollicis and masseter muscles in children. *Canadian Journal of Anaesthesia* 1990; **37**: 15–20.
3. Schwartz L, Rockoff MA, Koka BV. Masseter spasm with anesthesia: incidence and implications. *Anesthesiology* 1984; **61**: 772–775.
4. Carroll JB. Increased incidence of masseter spasm in children with strabismus anesthetized with halothane and succinylcholine. *Anesthesiology* 1987; **67**: 559–561.
5. Meakin G, McKiernan EP, Morris P, Baker RD. Dose–response curves for suxamethonium in neonates, infants and children. *British Journal of Anaesthesia* 1989; **62**: 655–658.
6. Meakin G, Walker RWM, Dearlove OR. Myotonic and neuromuscular blocking effects of increased doses of suxamethonium in infants and children. *British Journal of Anaesthesia* 1990; **65**: 816–818.
7. Goudsouzian NG. Relaxants in paediatric anaesthesia. In: Sumner E, Hatch DJ, eds. *Textbook of Paediatric Anaesthesia*. London: Baillière Tindall, 1989; 91–112.

Sir,—Thank you for the opportunity to reply to Dr Meakin's letter.

I did mention that the increase in stiffness may occur in other muscle groups, but did not go into great detail as the editorial was concerned primarily with the behaviour of the jaw muscles.

Much of Dr Meakin's argument is probably valid. However, the masseter muscle may not necessarily behave in the same way as the adductor pollicis muscle. For example, we found that the masseter muscle in children was more sensitive to suxamethonium, with an ED_{90} of 0.25 mg kg^{-1} [1]. We concluded at the time that "it is very unlikely that masseter spasm is due to a failure to block neuromuscular transmission at the masseter".

In addition, although Dr Meakin demonstrated that tone changes at adductor pollicis do not increase with large doses of suxamethonium, we found that suxamethonium increased masseter tone in a dose-related fashion up to 1 mg kg^{-1}. It would be interesting to assess tone changes at the jaw with larger doses.

The point that some children metabolize suxamethonium very quickly is a good one. In this situation, the jaw may appear stiff because the muscle has already begun to recover.

J. M. Saddler
Southampton

1. Plumley MH, Bevan JC, Saddler JM, Donati F, Bevan DR. Dose-related effects of succinylcholine on the adductor pollicis muscle in children. *Canadian Journal of Anaesthesia* 1990; **37**: 15–20.

TENSION PNEUMOTHORAX—DETECTION AND INCIDENCE

Sir,—We read with great interest the article by Laishley and Aps [1] and the subsequent comment by Kneeshaw [2]. The former, however, did not discuss methods of early detection and preventative measures.

It is difficult to maintain the head in a neutral position when a patient is moved from the supine to a lateral position, as the head tends either to flex or to extend. It is well known that flexion or extension of the head in patients with a tracheal tube may cause considerable movement of the tube [3] and may dislocate the tip of a left-sided, double-lumen tube over a distance of 27 mm in either direction [4]. Therefore one should check for displacement of the tip of the tube after a patient is placed in the lateral position, even if correct placement had been confirmed in the supine patient, by bronchoscopy or x-ray.

One can easily detect the onset of a ball valve mechanism by a change in lung compliance during manual ventilation, inability to perform right bronchial catheterization, and deflation of the cuff of the endobronchial tube before tension pneumothorax is established. These manoeuvres may be performed within minutes. Had this been the case in the patient reported, tension pneumothorax might have been prevented.

Fortunately, we have encountered only two cases of development of pneumothorax among some 30 000 general anaesthetics given at our hospital. We were able to detect pneumothorax in its early stages by minor changes in pulmonary compliance during manual ventilation and via frequent and deliberate auscultation of the lungs. These occurrences were treated successfully before circulatory derangements could ensue.

Y. Kubota
Y. Toyoda
H. Kubota
Osaka, Japan

1. Laishley RS, Aps C. Tension pneumothorax and pulse oximetry. *British Journal of Anaesthesia* 1991; **66**: 250–252.
2. Kneeshaw JD. Tension pneumothorax—Wrong tube? *British Journal of Anaesthesia* 1991; **67**: 222–223.
3. Conrardy PA, Goodman LR, Laing F, Singer MM. Alteration of endotracheal tube position: flexion and extension of the neck. *Critical Care Medicine* 1976; **4**: 8–12.
4. Saito S, Dohi S, Naito H. Alteration of double-lumen endobronchial tube position by flexion and extension of the neck. *Anesthesiology* 1985; **62**: 696–697.

Sir,—While it is pleasing to see that our article has raised some thought and correspondence, it must be remembered that it is always easy to be wise and critical after the event. We concluded, in addition to the other correspondents, that malposition of the endobronchial tube and cuff herniation, acting as a ball valve, were likely to be responsible for the development of tension pneumothorax. We hope that the publication of our article has at least served its purpose in reminding anaesthetists that tension pneumothorax should always be considered in the differential diagnosis of acute arterial desaturation during anaesthesia. Moreover, it underlines the value of pulse oximetry as mandatory monitoring during anaesthesia.

R. S. Laishley
London

FRESH GAS UTILIZATION IN THE CIRCLE SYSTEM

Sir,—With reference to the article on fresh gas utilization which appeared in October 1991 [1], it is difficult to visualize 100% utilization of fresh gases when the fresh gas flow exceeds 2–3 litre min^{-1}, especially when a minute ventilation of 8 litre min^{-1} is chosen. Assuming a respiratory quotient of 1.00 and a carbon dioxide production of 400 ml min^{-1} (for a 5% concentration of carbon dioxide in the expired air), the total amount of gases lost to the patient and to the carbon dioxide absorber cannot exceed 1 litre min^{-1}. In that instance, the remainder of the expired gas volume is available for patient ventilation. The addition of this amount of expired gas must dilute the fresh gases even if they enter the circle close to the patient.

In theory at least, therefore, 100% utilization of fresh gases can happen only if fresh gas flow equals the difference between the total ventilation and the expired minute volume after carbon dioxide absorption.

There is only one other consideration that is important in this calculation: the amount of gases allowed to leak, inadvertently or intentionally. If under measurable control, this may help achieve fresh gas utilization of 1.00 at a fresh gas flow greater than 2–3 litre min^{-1}. It is therefore doubtful if the solid line depicted in figure 2 is accurate beyond the 1–2 litre min^{-1} range.

P. U. Bhaskar
Belfast

1. Zbinden AM, Feigenwinter P, Hutmatcher M. Fresh gas utilization in eight circle systems. *British Journal of Anesthesia* 1991; **67**: 492–499.

Sir,—Dr Bhaskar's letter shows a misunderstanding of the term "fresh gas utilization" (FGU) as it had been defined in the CEN TC 215-Standard and in our publication. FGU is defined as the percentage of the fresh gas reaching the patient. Thus an ideal system can, at least theoretically, reach 100% FGU, provided that it is able to store the complete inflowing fresh gas in a reservoir and deliver it to the patient during inspiration; production of carbon dioxide does not affect fresh gas utilization. In the experiment, the 5% carbon dioxide which was used as a tracer gas was eliminated by the absorber, which may then have resulted in a small error of less than 5%. Leakage, as outlined in the discussion of the paper, may lead to an erroneously high fresh gas utilization. However, in this study all devices had been tested in this respect and showed a leak of less than 50 ml min^{-1}.

We are aware of the fact that fresh gas utilization may be defined in a different way. The definition used by CEN, however, is understood and the test procedure yields reproducible results. Using devices with high fresh gas utilization is of clinical relevance in order to obtain precise inspired concentrations, reduce costs for inhaled anaesthetics, and diminish the health and environmental hazards caused by wasted gases!

A. M. Zbinden
Bern

British Journal of Anaesthesia 1992; **68**: 453–455

BOOK REVIEWS

Aids to Anaesthesia: Basic Sciences, 3rd Edn. By T. E. J. Healy, M. J. Harrison and J. A. Thornton. Published (1991) by Churchill Livingstone, London. Pp. 263; indexed, illustrated. Price £9.95.

This *aide-memoire* is now in a third edition and observation at the examination rooms suggest it continues to be popular with examination candidates. However, I wonder if its terse style and attempt to include all potentially useful information makes it a suitable volume for last-minute revision, particularly for the ill-prepared. It would be of interest to compare pass rates of candidates with ownership of this and similar books and those who rely on standard texts.

A common complaint of examiners is that candidates are ignorant of basic knowledge, for example on the cardiovascular and respiratory symptoms or the pharmacology of anaesthetic agents. In this volume, respiratory physiology is reasonably well covered in 40 pages, but the cardiovascular system only merits 16 pages; the anaesthetic agents, both volatile and i.v., are given 15 pages—the same as clinical trials and statistics. The CNS is dismissed in 10 pages, while neuromuscular transmission is covered in six. It must be conjectured that this relative lack of balance may be confusing candidates. Events have, to a degree, overtaken this volume, and some of the information required by Part 2 F.C.Anaes. candidates, for example the pharmacology of the neuromuscular blockers, is contained in other volumes by the same authors. It is to be hoped that, in future editions, the subject matter in the various volumes will be rationalized.

The volume has an excellent index and contains many of the diagrams beloved of examiners. If these "condensed" aids to revision are for you, then this volume may be recommended highly, not least because of its price. Do not try to read it as you might a standard textbook, but dip into it when prompted by your revision programme.

C. D. Hanning

Care of the Critically Ill Patient in the Tropics and Subtropics, 1st Edn. By D. A. K. Watters, I. H. Wilson, R. J. Leaver and A. Bagshawe. Published by Macmillan, Basingstoke. Pp. 450; indexed; illustrated. Price £14.99; a special, low-priced edition will be available for sale in developing countries at a price equivalent to £5.00.

This 450-page manual is the first in its field—the application of the principles of critical care medicine to situations in which human and material resources are stretched to their limits. The authors, from the staff of a busy teaching hospital in Zambia, succeed in covering their subject clearly and comprehensively.

After an introduction which sets the reader's feet firmly on the ground, successive chapters deal with different organ systems from respiration to nutritional support. The authors succeed in communicating vital points, which they support with reasoned explanation. The style is clear, with abundant use of diagrams, tables, highlighted "key points" and many instructive clinical examples. This format may appeal to the harassed medical officer facing an emergency, but is equally suitable for the student who needs to master a topic. It is inevitable that, in trying to communicate many important concepts simultaneously, there is some degree of repetition, but this is not a great disadvantage. Each chapter concludes with a short list of important, accessible references for further study.

Readers from western countries will be interested and educated in reading the excellent sections on subjects such as snakebite, cerebral malaria, tetanus and eclampsia. The final 100 pages contain well illustrated descriptions of a wide range of practical procedures from tracheal intubation to burr holes and serve as a useful reminder for those in the front line! A brief formulary covers drugs used in critical care, and there is an excellent index.

In a book with such a high overall standard, it is difficult to single out one chapter, but my favourite is David Watters' "Organization and Management"—a classic piece of clear thinking and writing, which should be required reading for hospital administrators, and for anyone inclined to believe that critical care medicine is suitable only for the treatment of elderly patients with multi-system disease in materially rich countries!

The book carries the imprimatur and support of the World Federation of Societies of Anaesthesiologists, and wholly deserves them. It should be available at every hospital which has to deal with severely ill or injured patients, and will be of immense value to any western anaesthetist contemplating a spell of service overseas. Priced at £14.99, it represents excellent value, and would make a valued gift for a colleague overseas.

M. Dobson

Critical Care Practice. Edited by J. W. Hoyt, A. S. Tonnesen and S. J. Allen. Published (1991) by W. B. Saunders. Pp. 571; indexed; illustrated. Price: £28.50.

Unlike Europe and Australia, intensive care medicine in the U.S.A. is a fragmented discipline, with different training programmes and often separate intensive care units for each of the major specialties of anaesthesia, medicine and surgery. The editors say that the book is written with the trainee anaesthetist in mind, which one hopes would not be necessary in Europe. In his introduction to *Critical Care Practice*, Peter Safar rightly deplores these divisions, and gives as the *raison d'être* for this book the need to involve anaesthetists more closely in medical and surgical intensive care.

There are three sections. The first describes the principles of organ–system support and monitoring; the second, specific organ–system failures; and the third, particular topics of relevance to intensive care practice such as resuscitation, trauma, burns, obstetrics and management. The book starts with the assessment of critically ill patients, and discusses demographic analyses and scoring systems. The "TISS" score is for some reason referred to as the Therapeutic *Index* rather than *intervention* scoring system. It would have been useful to have emphasized the importance of, and difficulty of measuring, physiological reserve at this point, with a discussion of the effects of chronic health impairment and severity of illness on survival and quality of life. The assessment of cost–efficacy of intensive care appears in the chapter on administration at the end of the book, receiving only three paragraphs; it might more appropriately have been amplified at the beginning.

The second chapter, entitled "Initial Stabilisation", is surprisingly long on airway management, providing a level of detail appropriate to someone who has never practised anaesthesia. Sedation of patients for ventilation is discussed in terms of managing the "combative patient", and it is not until the reader reaches chapter 28 on Pain Management that there is any discussion of comfort care and drug therapy. As this is a text for trainees, I would have liked more emphasis on the difficulties of making a diagnosis in critically ill patients, as the commonest error in clinical intensive care practice is to provide organ–system support without dealing effectively with the underlying problems. The importance of establishing a plan of action is given due weight, although the advice to encourage patients to move out of bed may seem strange to those of us with sufficient resources to admit only the most severely ill patients.

There then follow three useful chapters on respiratory, cardiovascular and neurological support. Weaning from mechanical ventilation is discussed well. Surprisingly, the section on oxygen delivery is limited to one and a half pages, and does not discuss the problem of interpreting oxygen transport variables in sepsis. Discussion of vasoactive drugs is confined mostly to dopamine, dobutamine and amrinone; dopexamine is not mentioned and adrenaline is dismissed; no doubt this reflects a bias towards coronary care. I would have liked to have seen more extensive discussion of pathophysiology, although to some extent this is amplified in the second part of the book. The final two chapters of this first section are on monitoring, and are well presented and helpful.

The second section examines specific organ–system failures. It might have been advantageous to discuss objective criteria for defining such failures either here or in chapter 1. This section is generally well written, although there are some omissions. Brain death is discussed as an entity without separating cortical from brainstem death; the chapter on renal failure does not mention intrarenal oxygen consumption; the chapter on infectious diseases gives only one paragraph to prevention, and none to selective decontamination or the use of sucralfate in modifying gastric colonization; and the potentially important chapter on gastrointestinal disease is weak on pathophysiology, endotoxin leak and the liver as a potential source of vasoactive mediators. The chapter on endocrinology is good.

The final section of the book covers a variety of clinical situations, and it is here that we encounter a chapter on the problem which best typifies intensive care practice—multiple organ failure—which is dismissed in four and a half pages. It is difficult to know what to make of this chapter, and perhaps one should have some sympathy for the author who has, in effect, been asked to summarize the whole of intensive care and has then been confined to mixed company at the back of the room. He has at least tried to define his subject, although without examining Knaus' definitions. Both obstetrics and AIDS are covered, briefly but adequately. The chapter on pain management devotes considerable space to patient-controlled techniques, again demonstrating that American intensive care is often European ward care; surprisingly, there is no discussion of the use of non-steroidal anti-inflammatory drugs, if only to caution against their use; and no warning about the accumulation of morphine-6-glucuronide in patients with renal impairment. The two final chapters are on administration and transport; both are somewhat limited in scope, and should have provided didactic advice to the reader.

There is a comprehensive index. Diagrams are mostly clear and apposite, but the reference sections accompanying each chapter are often rather short, although adequate to support an educational text. The price is reasonable, particularly for a hard-back.

This textbook will no doubt appeal to the audience for whom it was written—American anaesthetists wishing to develop their knowledge of intensive care. There is certainly much in it which is good; European doctors of all specialties and ICU nurses will find it helpful as a reference during their ICU training, although it should be read critically. I would recommend it to intensive care units as a text which contains something of value for everyone.

J. F. Bion

Clinical Practice of Regional Anesthesia. Edited by P. P. Raj. Published by Churchill Livingstone, Edinburgh. Pp. 526; indexed; illustrated. Price £70.00.

This book is based on the *Handbook of Regional Anesthesia,* which was published originally in 1985, and retitled, in view of the extensive alterations which have been made. Professor Raj has assembled an impressive list of contributors from the world of regional anaesthesia although, understandably, the majority are from the U.S.A.

The book is divided into four sections and does not get off to an auspicious start. I did not find the chapter on Historical Aspects particularly inspiring and the discussion of preoperative evaluation of the patient could be transposed to any textbook of general anaesthesia; it would have been more relevant to concentrate on the particular aspects of preoperative evaluation relevant to regional anaesthesia. Thereafter, matters improve considerably. The second section, entitled "Equipment, Monitoring and Drugs," covers the basic physiology and pharmacology clearly. In the third section, techniques are covered in detail. The descriptions are generally clear and unambiguous. I hope that merely reading about a technique and then proceeding to carry it out is largely a thing of the past, but there is sufficient detail to allow this, should it be essential. The illustrations are black and white line drawings, with some containing one additional colour for clarity. They are drawn well and are clear, although perhaps they do not quite match the very high standards which we have seen in others texts. The final section deals with specific situations such as obstetrics, acute and chronic pain, and complications. The chapters are all referenced extensively and well indexed.

As one would expect in what is basically an American text, the emphasis is slightly different from attitudes in the U.K. For example, although it is stated that bupivacaine is not recommended for i.v. regional anaesthesia in the U.S., I would expect a much stronger condemnation in the U.K. One of the contentious areas in the U.K. at present concerns the use of extradural infusion after operation and the degree of supervision which this requires. This is not discussed at much length—perhaps the medico–legal situation in the U.S. makes it unthinkable for this to be carried out in less than ideal conditions.

There have been many texts produced in recent years in response to an increased interest in this subject and the standard of several of these is extremely high. This book may find a gap in the market between the less expensive but less complete shorter texts and the encyclopaedic major works. It is too comprehensive for Fellowship candidates to be expected to read it completely, although many will it a useful source of reference both on fundamental principles or for guidance for a particular block. Overall, I enjoyed reading it and feel that some experts may wish to have their own copy. It is not as comprehensive as some of the larger texts, or quite as well illustrated, although this latter comment is really not a serious criticism. On the other hand, it is considerably less expensive than the larger texts and certainly easier to read from cover to cover. This would be a useful addition to a departmental library.

W. A. Chambers

A Rational Basis for Anesthesiology. By G. Dal Santo. Published by Piccin, Padua. Pp. 933; indexed; illustrated. Price £48.00.

This book starts with a curious statement noting the author's "disillusionment of medical politics and academic intrigues" on the same page as a quotation from Virgil: "Lucky is he who knows what is going on". I had doubts about the quality of a book of over 900 pages written by a single author, particularly one who has published little original work in recent years. My worries were partly assuaged on reading the book, as it is clear that the author's intention was to write a basic textbook of anaesthesia based on a series of lectures given to residents.

The choice of topics included in the book ranges from principles and functions of anaesthetic equipment to anaesthetic drug actions and reactions. The level at which the material is covered is fairly simple and many of the numerous illustrations are taken from classic papers in the anaesthetic literature in the 1960s and 1970s. It was pleasing to see many of the original manuscripts acknowledged for their important contributions to our understanding of anaesthetic practice. This book reminds me of *Scientific Foundations of Anaesthesia* by Scurr, Feldman and Soni, but at a more elementary level. I cannot see a ready market for this book in the United Kingdom. Nevertheless, I am filled with admiration for the industry of an author who has written a book of this length.

G. M. Hall

Drugs in Anaesthetic Practice, 7th Edn. By M. D. Vickers, M. Morgan and P. S. J. Spencer. Published by Butterworth–Heinemann, Oxford. Pp. 537; indexed; illustrated. Price £60.00.

Over successive editions, this book has become "necessary reading" for every trainee anaesthetist. Nowhere else can such a comprehensive account be found of drugs used by anaesthetists in the United Kingdom. A new edition is, therefore, a significant event.

The book has changed; with the death of Geoffrey Wood Smith and the retirement of Professor Schnieden, Professor P. S. J. Spencer, Professor of Pharmacy and Pharmacology at the Welsh School of Pharmacy and Dr Malwyn Morgan, Reader in Anaesthetic Practice at the Royal Postgraduate Medical School, London, have joined Professor Vickers as co-authors.

As may be expected from such radical changes, the book itself has been extensively remodelled. It is slimmer and smarter, with an attractive cover and a bolder, easier to read typeface. There are some 60 pages fewer, largely because of the long-overdue abandonment of seemingly endless tables of U.K. and U.S.

equivalent names. These are reduced to a single page of drug names which really do differ significantly.

Following its long-established formula, the book opens with a chapter on General Pharmacology which, considering its brevity, is excellent. I would doubt the wisdom, however, of referring anaesthetic trainees to Gibaldi and Perrier's standard text on pharmacokinetics. Before seeking it out in the library, they should be aware that this superb volume, a "bible" to clinical pharmacokineticists, consists largely of equations and therefore may not be quite what they need.

A long-standing criticism of this book has been its lack of balance, such that descriptions of some drugs of prime importance have been somewhat sketchy, while drugs of little relevance to anaesthetists were given equal space. Thus accounts of vitamin D and prilocaine both occupied one page. To some extent, the new edition is an improvement. Although vitamin D, together with several other agents of marginal interest to anaesthetists, has disappeared altogether, we still find the pharmacokinetics of primaquine given the same space as inhalation anaesthetic agents. Similarly, the clathrate theory of anaesthetic action, about which little has been written in the past 20 years, still is given pride of place over more modern concepts.

In a book of this type, references present a real problem to the authors. Reference-free text is easier to read, and trainees reading for Part 2 are unlikely to be much interested in source material. However, many readers welcome key references at the end of each section, with indications as to where to go for a fuller account. In some chapters, such as "Inhalational Anaesthetic Agents", this philosophy is applied to great effect. By contrast, in "Neuromuscular Blocking Agents", references on atracurium are reduced from three to two, and other drugs have none.

Of course, such criticisms are far easier to make than to avoid, and the authors must be commended for the general quality of this text. Coverage is encyclopaedic, and the excellent index enables the reader to find information on almost any topic concerned with anaesthetic pharmacology. Many new drugs, including some which have not yet appeared in clinical practice, have found a place, and these sections make fascinating reading.

This new edition should be on every departmental librarian's list, and every trainee in anaesthesia should have a personal copy.

C. J. Hull

Anaesthesia, Analgesia and Intensive Care, 1st Edn. Edited by A. P. Adams and J. N. Cashman. Published by Edward Arnold, Sevenoaks. Pp. 313; indexed; illustrated. Price £14.95.

Seventeen authors contribute to this short text, which is edited by Professor A. Adams and Dr J. Cashman and is aimed at teaching anaesthesia to undergraduates. The main justification for the book appears to be that the requirements of medical students were not served by the existing range of text books. All the authors are on the staff of the London Teaching Hospitals and this text may well become known as a London undergraduate anaesthetic book.

The text starts with an extremely wide ranging introduction suitable for a lay novice to anaesthesia and then proceeds with basic anaesthetic physiology. The chapters are packed with facts and oversimplification is rife. Cardiovascular, respiratory, renal and gastrointestinal physiology, neurophysiology and haematology are compressed into 22 pages. There are many words, but few diagrams. It is difficult to see the value of two paragraphs only on renal physiology and half a page on gastrointestinal physiology, which ranges from the volume and acidity of gastric contents through regurgitation and concludes with the use of cisapride. The pharmacology chapter includes such quaint drugs as methohexitone and trichloroethylene, the relevance of which to undergraduate teaching must be remote. There is, however, a very good section on opioids. The attempt to cram as much information as possible into a short space has resulted in lists and note form in the main text. This might have been preferable as a table.

The process of anaesthesia inevitably contained some repetition from the previous pharmacology chapter. Total i.v. anaesthesia was discussed together with all its advantages but, for some reason, the disadvantages of this technique were excluded.

There is an excellent chapter on monitoring, but more tables and charts would perhaps help the undergraduate.

The difficult subject of fluid electrolyte and acid–base balance contains some misleading statements, such as that potassium should be given no faster than 40 mmol h^{-1}. It would be preferable to err on the side of caution and recommend to a medical student a smaller hourly intake than this.

Oxygen therapy is covered admirably, but I wonder if the authors intended to suggest that "respiratory narcosis" may result from too high an inspired concentration of oxygen, or if they felt that some explanation of carbon dioxide narcosis might be more relevant.

The clear diagrams of anaesthetic apparatus are excellent, but I suspect some students might benefit from an explanation of the difference between kPa, mm Hg, torr and bar. There is perhaps excessive emphasis on scoring systems in the section on preparation of patients for anaesthesia and surgery. Clear line diagrams in the chapter on practical procedures are extremely useful, although the inclusion of an extremely old fashioned introducer as an aid to intubation is puzzling. More than an intradermal weal of local anaesthetic is likely to be required for arterial cannulation, as I have discovered to my cost in the past. I suspect that undergraduates would also like to know of the existence of triple lumen catheters for central venous cannulation.

In the obstetric chapter, a certain amount of circumlocution—"the pregnant woman's inability to keep her gastric contents in her stomach"—was balanced by very good tables of basic resuscitation of the newborn. Paediatric anaesthesia was discussed in one of the longer chapters, which includes a description of equipment to be used at a level perhaps slightly beyond that suitable for undergraduates. Perhaps a little more advice should be given on the alternatives to opioid analgesia in very young children in whom their use may be dangerous. The chapter on life support and cardiopulmonary resuscitation was clear and dogmatic, as it should be.

Some vivid writing crept into the section on head injury, where the author tells us that some U.S. states have little experience of penetrating head wounds because of the population's preference for magnum "ammunition"—the victims simply had no heads! In discussion of brainstem death, it is suggested that most patients are disconnected from their ventilation after this diagnosis is made. This is probably no longer true, and perhaps for the next edition considerations of organ donation should be included. The chapter on anaesthetic complications is most helpful, but that on pain relief probably requires expansion. In this first edition, 17 pages were used to cover the definition, classification and measurement of pain, with discussion of acute chronic and cancer pain management. This section is probably too slim for its outstanding importance. To cover intensive care in 20 pages is a similarly daunting task, but very good use is made of lists and tables, for example for the causes of respiratory failure, modes of ventilation and effects of malnutrition, which made this chapter extremely informative.

Overall, this book provides a good introduction for medical students with only minor problems of an edited work such as some repetition (never a bad feature) and variability in presentation and emphasis. I feel sure this book will be read widely and achieve its objective. The next edition should be even better.

S. M. Willatts

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"I would have everie man write what he knowes and no more."—MONTAIGNE

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EDITORIAL I

COLLEGIATE DEVELOPMENTS

On 16 March 1992, it was announced that Her Majesty Queen Elizabeth II has granted to the College of Anaesthetists a Charter, and that henceforth the body will be known as the Royal College of Anaesthetists. There are two separate features implied in the statement. First, the Charter gives the privilege of establishing a new and independent College out of the previous College of Anaesthetists which was legally a part of the Royal College of Surgeons of England. Second, the Royal prefix in the title is an acknowledgement of a body perceived to have sufficient standing to justify that level of recognition.

To some, statements about a Royal College may read like gobbledegook, but there are important implications for the health of anaesthesia and, I believe, the care of patients. The granting of Charters and of Royal prefixes can be traced to mediaeval times in the United Kingdom. The Royal College of Surgeons of England, from which the Royal College of Anaesthetists has emerged, is itself descended from the mediaeval Barber Surgeons and moved through various stages to become a Royal College in 1800. There are presently three Royal Colleges of Surgeons [England, Ireland and Edinburgh] and of Physicians [London, Ireland and Edinburgh], a Royal College of Physicians and Surgeons of Glasgow and a Royal College of Obstetricians and Gynaecologists. The "modern" Royal Colleges embrace General Practice, Pathology, Psychiatry and Radiology. The College of Ophthalmologists has a Charter but does not, at the moment, enjoy the Royal prefix.

The Royal College of Surgeons of Edinburgh seems to have had the easiest birth of the "ancient" Colleges, in 1505, and well illustrates the ethos. Up to 1505, the Barbers and Surgeons of Edinburgh included unreliable and ill disciplined individuals who lacked public esteem and, in some cases, were a source of public danger. Their Seal of Cause of 1505, to the craftsman Surgeons and Barbers in the town, ensured that only the new Royal College of Surgeons could give a licence to practice. Thereafter, apprentices were required to be examined in anatomy, reading and writing and in the signs of the zodiac [to enable prognosis]. An additional attempt at setting a standard was the restriction of entry for the apprenticeship to the sons of craftsman, sons of the nobility and anyone marrying the daughter of a Surgeon [provided she was a "clene virgin"]. Certain privileges were granted in the form of access to the bodies of hanged individuals and exclusive rights to trade in aqua vita. Although the Charter brought to the town a much more reliable craft, the Physicians of Edinburgh, after several false starts, successfully petitioned for their Charter because of "frequent murders committed universalie by quacks, women, gardeners and others grossly ignorant...". They also drew attention to "the unlimited and unaccountable practice of Chirurgeons, Apothecaries and Empiricks pretenting to medicine... all these undertaking the cure of disease without the assistance of Physicians" [1].

Thus Charters were, and are, given to bodies so that the public interest might be better fulfilled. To be a Fellow of a College offers privileges, but also imposes responsibilities to ensure that the corporate standards of the Fellowship are maintained and sustained. Thus there is a system of checks and balances in the patient's interest, but the doctor has the privilege of working to an established standard.

By a happy coincidence, the Royal College of Anaesthetists is not the only one of the genre. There have been Faculties in Ireland, Australasia and South Africa for many years. These, with the American Board and the Anaesthetists of the Royal College of Physicians and Surgeons of Canada, have formed a standing biennial conference on a wide range of issues on which reciprocity of diplomas is based. That conference will be in London this year, to coincide with the celebration of the new Royal College. Meantime, it has been announced that our Australasian colleagues, having agreed their memorandum and articles of association, are now established as the Australian and New Zealand College of Anaesthetists. This new body succeeds the Australasian Faculty. Although it will be housed within the Royal Australasian College of Surgeons, at Melbourne, it is legally independent of it.

Although not part of the biennial conference, the College of Anaesthetists of Hong Kong goes from strength to strength. A Faculty of Anaesthetists has been set up in the College of Physicians and Surgeons of Pakistan. News has also reached us of a Royal College of Anaesthetists in Thailand. Finally, meetings are commencing to explore the possibility of a "Board" for anaesthesia in the European Community; its function is likely to be that of an evolving quality assurance body that will, in the first instance, establish a minimum standard in practice and training for the countries of the Community.

All these exciting developments testify to the increasing importance of the discipline of anaesthesia in society throughout the world. For us in Britain and also, I know, for our colleagues in Australia and New Zealand, the new status of our Colleges will not be seen as a reason for free-wheeling on past glories. Instead, the challenge to offer, in a totally ethical context, the best that is possible in good, reliable and safe practice is renewed.

From the Royal College of Anaesthetists in London we assure colleagues throughout the world of our rededication to the international cause of anaesthetic training and standards.

Alastair A. Spence
President
Royal College of Anaesthetists

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EDITORIAL II

LIVER DISEASE AND DRUG DISPOSITION

The liver is the main organ responsible for the metabolism of xenobiotics, including drugs. In liver disease, handling of drugs by the liver may be disturbed greatly by several mechanisms, including, principally, altered absorption, disposition (elimination) and distribution. The effect of drugs may be altered also in patients with hepatic dysfunction. It has been recognized for many years that some patients with liver disease are especially sensitive to the effects of some drugs, in particular sedatives such as benzodiazepines. This would appear to be a result of altered pharmacological responsiveness, rather than derangement of pharmacokinetics [1].

Absorption of drugs and distribution within the body may be disturbed in liver disease, leading to abnormal bioavailability. For example, the absorption of the beta blocker bisoprolol appears to be reduced in patients with advanced liver disease so that, although metabolism is impaired also, blood concentrations do not increase as much as expected [2]. Because of associated hypoalbuminaemia, drug binding may be reduced in liver disease, increasing the proportion of free drug available for metabolism; this also tends to normalize pharmacokinetics in patients with reduced metabolic capacity [3]. Reduced plasma protein binding also influences penetration of drugs into tissues and drug distribution. Obviously, the increased total body water found in liver disease, particularly in those with ascites, increases the volume of distribution of hydrophilic substances. In cholestatic liver disease, reduced bile acids in the intestine may impair drug absorption, and protein binding of drugs may be influenced by increases in the concentrations of bilirubin and bile acids in plasma, again affecting drug distribution and metabolism. Increased intrahepatic bile acid concentrations may also affect drug metabolizing enzymes [4].

The dominant factor affecting drug pharmacokinetics in patients with liver disease is abnormal drug disposition, and a study in this issue of the Journal by Bower and colleagues [5] illustrates well some of the complexities affecting drug disposition. They found that the aetiology of hepatic disease affected the disposition of alfentanil. Although some of this difference may have been caused by slightly more severe disease in patients with alcoholic liver disease, differences in drug disposition would be expected to vary with liver pathology, as discussed below.

Drug disposition is influenced by many factors in patients with liver disease, the most important of which are abnormal (usually reduced) liver blood flow, porto–systemic shunting and impaired metabolic capacity. These factors vary from patient to patient and their importance varies from drug to drug. Classically, drugs may be classified into three main groups with reference to hepatic metabolism: "high risk", "limited risk" and "low risk" drugs [6]. The degree of risk depends largely upon the dependence of drug metabolism on liver blood flow. High risk drugs such as glyceryl trinitrate [7], propranolol [8], chlormethiazole [9] and pentazocine [10] have a high hepatic extraction—normally more than 60% of available drug in a single pass. The disposition of such drugs after oral administration is highly dependent upon liver blood flow, with first-pass elimination limiting systemic availability of absorbed drug. In patients with liver disease, liver blood flow is generally, although not invariably, reduced (again depending upon aetiology) and porto–systemic shunting allows blood draining from the splanchnic circulation to bypass the liver. Both of these factors may have a profound effect on drug pharmacokinetics, leading to high peak drug concentrations with less effect on drug half-life [6]. If such high risk drugs are to be prescribed in patients with liver disease, the dose to be administered should be reduced, rather than the frequency. The pharmacokinetic profiles of high extraction drugs after parenteral administration (which reduces the effect of high first-pass extract by allowing drug access to the systemic circulation without passing through the portal vein) might be expected to be relatively unchanged in patients with hepatic disease. In reality, factors such as decreased hepatic uptake of drugs and intrahepatic shunting complicate the situation [11].

Drugs which have an extraction of less than 30% in a single pass through the liver depend much less on liver blood flow and more on the metabolic capacity of the liver. Systemic bioavailability of these agents is much greater than for the high extraction drugs. Low extraction or limited risk drugs include chloramphenicol [12], theophylline [13] and outdated agents such as antipyrine [14] and aminopyrine [15], the clearances of which are now used as dynamic liver function tests. Caffeine is also a limited risk drug [16] and has been used recently in clearance studies to assess liver function. Although several sedatives, including diazepam [14] and phenobarbitone [17], are low extraction drugs, they should perhaps not be considered limited risk agents, as patients with liver disease show increased end-organ sensitivity.

Low extraction drugs, although dependent on the metabolic capacity of the liver rather than its blood flow, may demonstrate differences in metabolism in patients with liver disease because of the metabolic pathways involved. Oxidation of drugs (a phase I reaction) is carried out principally by the cytochrome P450 enzymes, which are situated predominantly in zone 3 (centrilobular area) of the hepatic lobule

[18, 19]. In contrast, enzymes responsible for conjugation (phase II reactions), such as the glucuronyl transferases, are plentiful in zone 1 (the periportal area). Enzymes situated in zone 3, an area more prone to hypoxia, appear to be affected more in liver disease than those in zone 1 and there is some evidence that glucuronidation, a phase II reaction, is relatively well preserved in patients with liver disease, unlike phase I reactions [19]. In patients with some liver diseases, for example those caused by ethanol, enzyme induction may be present and influence drug metabolism. It is clear, therefore, that the "metabolic capacity" of the liver is not a homogeneous entity in patients with liver disease, but depends upon the metabolic pathways involved. For example, the pharmacokinetics of drugs such as lorazepam and morphine appear to be relatively normal in patients with liver disease, even though they are metabolized within the liver (because they undergo glucuronidation). Despite this, however, increased end-organ sensitivity to these drugs should place them within the "limited" rather than the "low risk" group, despite their pharmacokinetic profiles.

The pharmacokinetic profiles of low extraction drugs tend not to show particularly high peak blood concentrations, but rather increased half-life. Theoretically, it should be the frequency of drug administration that should be reduced, rather than the dosage.

It should be remembered that, whilst impaired hepatic drug disposition tends to prolong or increase the effect of many drugs, prodrugs, which commonly are activated by the liver to active compounds, may be handled abnormally [20] and have less effect.

The disposition of some drugs is relatively unchanged in patients with severe liver disease, for various reasons: for example, penicillins are eliminated principally by the kidneys, whilst other agents such as digitoxin and phenytoin, although metabolized by the liver, have increased concentrations of free drug available for metabolism because of reduced protein binding [6]. Relatively preserved glucuronidation in liver disease mitigates against abnormal metabolism of some drugs, as discussed above.

The mechanism whereby normal disposition of some drugs occurs in patients with liver disease remains unclear. Whatever the reason for normal disposition in liver disease, such drugs may be considered low risk substances; these include cimetidine [21], digoxin [22], spironolactone [23] and frusemide [24]. Where possible, drugs in this group are the agents of choice for patients with liver disease, although again such factors as altered end-organ sensitivity, drug distribution or absorption and route of administration may influence their therapeutic effect.

In conclusion, drug handling in patients with liver disease is complex and involves many factors. Drug disposition depends upon such properties as the degree of first pass hepatic extraction and the enzymes involved in metabolism. Despite the theoretical rationale behind the pharmacokinetic changes predicted for various classes of drugs, individual variations in drug disposition in patients with liver disease makes monitoring of the patient's drug response and plasma drug concentrations (where possible) prudent. Even when disposition is unaffected, other factors, including increased patient sensitivity to the drug, need to be considered.

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ORIGINAL ARTICLES

EFFECTS OF DIFFERENT HEPATIC PATHOLOGIES ON DISPOSITION OF ALFENTANIL IN ANAESTHETIZED PATIENTS†

S. BOWER, J. W. SEAR, R. C. ROY AND R. F. CARTER

SUMMARY

We have studied the influence of different hepatic pathologies on the disposition of alfentanil in 23 unpremedicated patients (six healthy control subjects, six patients with liver dysfunction of alcoholic aetiology and 11 patients with non-alcohol related liver disease). All patients received a bolus of alfentanil 500 µg i.v. as supplement to 67% nitrous oxide and isoflurane in oxygen anaesthesia. Plasma drug concentrations were measured in venous blood samples at intervals up to 24 h by radioimmunoassay and protein binding was determined by equilibrium dialysis. Kinetic estimates were determined using non-compartmental analysis. Patients with non-alcoholic liver disease had lesser plasma clearance (114.8 (range 66.8–213.5) ml min^{-1}) than the alcoholic group (158.8 (100.0–220.7) ml min^{-1}) or controls (187.4 (125.2–269.5) ml min^{-1}). In all three groups, there was considerable intersubject variability, with a bimodal distribution in the non-alcoholic group. This group also had a smaller apparent volume of distribution at steady state. Mean residence time was prolonged in the alcoholic group compared with controls (284.9 (217.8–362.2) min vs 226.8 (201.2–250) min). Protein binding was decreased in the alcoholic group compared with controls (84.9 (SD 4.2)% vs 89.3 (2.1)%); this was attributable to a lesser plasma α_1-acid glycoprotein concentration (0.55 (0.18) g litre^{-1} vs 0.89 (0.21) g litre^{-1}). Free drug clearance was reduced in both liver dysfunction groups compared with controls.

KEY WORDS

Analgesics: alfentanil. Liver: disease. Pharmacokinetics: clearance, distribution.

Alfentanil undergoes extensive metabolism in the liver, by microsomal oxidative N-dealkylation. It might therefore be expected that alterations in drug disposition would be seen in the presence of liver disease.

In a previous study, Ferrier and colleagues [2] demonstrated a significant reduction in the plasma protein binding and plasma clearance of alfentanil in patients with alcoholic cirrhosis. The apparent volume of distribution at steady state (V^{ss}) was unaltered. Plasma albumin concentrations were decreased, but there was no difference in the plasma concentrations of α_1-acid glycoprotein, an acute phase protein that is an important binding site for alfentanil [3].

Blaschke [4] suggested that, as different types of liver disease vary in their relative emphases on changes in liver cell function, liver blood mass and liver blood flow, so pathological differences may present as a spectrum of altered pharmacokinetics for a given drug. For example, a drug with clearance in the liver, being mainly flow-dependent, is affected more than a capacity-limited drug under circumstances in which liver blood flow is more compromised than hepatocellular function (and *vice versa*).

Little work has been presented yet which investigates this hypothesis. Often the term "cirrhosis" has been used as a general description for patients with liver disease—irrespective of the aetiology.

In the present study, we have examined the disposition and protein binding of the opioid alfentanil used as part of a balanced anaesthetic technique in patients with hepatic dysfunction of different aetiologies: alcoholic liver disease ($n = 6$) or non-alcoholic cirrhosis ($n = 11$), and compared these with data from six healthy, anaesthetized patients with no clinical or laboratory evidence of liver disease.

PATIENTS AND METHODS

All patients were unpremedicated, and gave their informed consent to the study, which was approved by the local Hospital Ethics Committee. Seventeen patients with liver dysfunction of alcoholic ($n = 6$) or non-alcoholic aetiology were undergoing endoscopic

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This article is accompanied by Editorial II.

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TABLE I. *Patient and biochemical data for the three patient groups (mean (range or SD)). AAG = α_1-Acid glycoprotein; AST = aspartate aminotransferase.* $P < 0.05$ *compared with:* * *control group;* † *standardized value*

	Normal range	Control group	Alcoholic liver disease	Non-alcoholic liver disease
n	—	6	6	11
Age (yr)	—	46 (28–64)	55.5 (42–70)	52.5 (26–78)
Weight (kg)	—	81 (17.3)	71.6 (15.7)	67.8 (15.6)
Sex (M:F)	—	5:1	5:1	6:5
Albumin (g litre^{-1})	38–48	41.8 (1.9)	36.5 (6.7)	38.2 (5.0)
AAG (g litre^{-1})	0.55–1.40	0.89 (0.21)	0.55 (0.18)	0.76 (0.32)
AST (iu litre^{-1})	< 37	all < 37	48 (30–73)	50 (16–77)
Bilirubin (µmol litre^{-1})	< 17	all < 17	58 (10–176)	20 (11–43)
Prothrombin time > control (s)	—	—	4.2 (2.9)*	2.2 (2.4)

ligation of oesophageal varices; six control subjects were undergoing upper endoscopic investigations or body surface surgery of similar duration.

The aetiologies of the non-alcohol-related liver dysfunction group were micro/macronodular cirrhosis ($n = 3$), cirrhosis secondary to portal vein thrombosis ($n = 3$), cirrhosis secondary to chronic active hepatitis ($n = 2$), cryptogenic cirrhosis ($n = 2$) and primary biliary cirrhosis ($n = 1$). A diagnosis of alcoholic related dysfunction was made only on the basis of a positive history of alcohol abuse, and positive histological changes (enlargement and disorganization of mitochondrial cristae, decreased number of intramitochondrial inclusion bodies, presence of hyaline Mallory Bodies, and increased number of perioxisomes).

Anaesthesia was induced with etomidate 12–20 mg, the trachea intubated after neuromuscular block with vecuronium 0.1 mg kg^{-1}, and anaesthesia was maintained with 60–70% nitrous oxide in oxygen supplemented by isoflurane (< 1.0%). When stable anaesthesia had been attained, analgesia was provided by a bolus dose of alfentanil 500 µg given i.v. over 20 s into a flowing peripheral infusion.

Blood sampling and alfentanil analyses

Peripheral blood was sampled from the contralateral arm before injection of alfentanil, and then at regular intervals from 2 min to 24 h: at 2, 4, 6, 8, 10, 15, 20, 25, 30, 45 and 60 min, every 30 min to 6 h and then at 8, 20 and 24 h. Blood was separated by centrifugation, and the plasma stored at −20 °C until assay for alfentanil by a radioimmunoassay [5]. The sensitivity of the assay was 2 pg ml^{-1}, and the intra-assay coefficients < 10% over the concentration range measured. ^{3}H-Alfentanil and the rabbit anti-alfentanil antibody were obtained from Janssen Pharmaceutica BV, Beerse, Belgium. With this antibody there is no cross-reactivity to any of the known metabolites of alfentanil [6]. Each sample was assayed in duplicate.

Drug binding to plasma proteins was measured at 37 °C and pH 7.4 using equilibrium dialysis against phosphate buffer 1 mol litre^{-1} [7].

Laboratory investigations

All patients had the following biochemical indices measured: total plasma protein, serum albumin, serum bilirubin and aspartate aminotransferase concentrations, and prothrombin time (SMAC parallel analyser). α_1-Acid glycoprotein (AAG) was measured by radioimmunodiffusion.

Kinetic analyses

Plasma concentration–time data were analysed by non-compartmental methods. The area under the concentration–time curve ($AUC_{0-\infty}$) and its first moment were calculated using the linear trapezoidal rule. The area under the curve between the last data point (C_t) and infinity was calculated as C_t/k, where k = elimination rate constant determined by non-linear regression analysis. Mean residence time (MRT), clearance (Cl_P) and apparent volume of distribution at steady state (V^{ss}) were calculated according to Benet and Galeazzi [8]. Free drug kinetic parameters were obtained by dividing Cl_P and V^{ss} by the free drug fraction to give Cl_Pu and V^{ss}u.

Statistical analyses

Overall differences between groups were determined using ANOVA, and between pairs of groups using the Mann–Whitney U test. Data are shown in the tables as mean (SD) and range. Significance is assumed at $P < 0.05$.

RESULTS

Anaesthesia and the postoperative period were uneventful in all subjects. There were no significant differences between the three patient groups in age and weight, but there was a greater number of female subjects in the group with non-alcohol related hepatic dysfunction. Baseline biochemical data are shown in table I.

Examining total drug kinetics, there were significant differences in clearance between the three groups (fig. 1). This was reduced in the non-alcoholic group compared with controls ($P < 0.05$). Inspection of the data suggested a bimodal distribution of clearance values in the former group, with smaller estimates in patients with cirrhosis secondary to portal venous thrombosis ($n = 3$), micro/macronodular cirrhosis secondary to post-transfusion hepatitis B ($n = 1$) and autoimmune aetiology ($n = 2$). MRT was prolonged in the alcoholic group compared with controls ($P < 0.05$). There was a signifi-

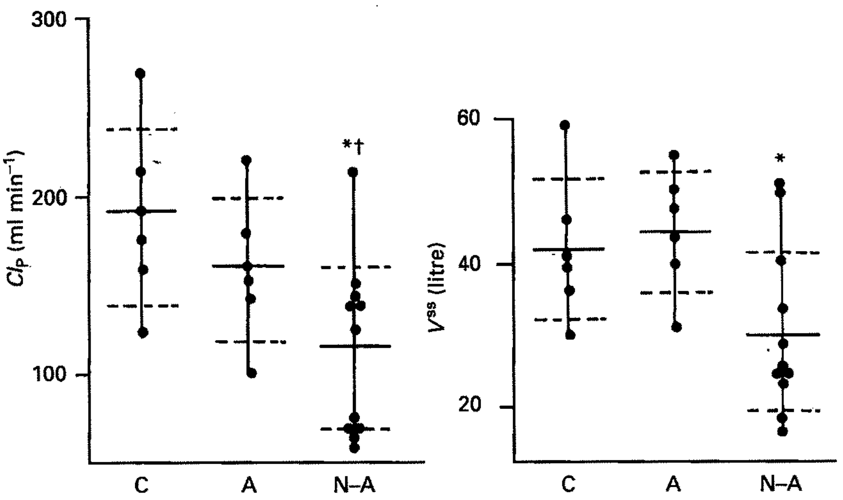

FIG. 1. Individual values for alfentanil clearance (Cl_P) and apparent volume of distribution at steady state (V^{ss}) in the three patient groups. —— = Mean; – – – = 1 SD. C = Control (healthy patients); A = patients with liver dysfunction of alcoholic aetiology; N–A = patients with non-alcohol related liver disease. $P < 0.05$ compared with *control; †patients with alcohol-related liver disease.

TABLE II. *Derived pharmacokinetic parameters (mean* (SD) *[range]) for binding, elimination half-life* ($T_{\frac{1}{2}}^{el}$)*, mean residence time (MRT), plasma clearance* (Cl_P) *and apparent volume of distribution at steady state* (V^{ss})*. Also shown are the free drug estimates for* Cl_P *and* V^{ss}. $P < 0.05$*: * compared with control group; † between liver dysfunction groups*

	Control group	Alcoholic liver disease	Non-alcoholic liver disease	ANOVA
Binding (%)	89.3 (2.1)	84.9 (4.2)*	86.4 (3.1)	ns
Total drug				
$T_{\frac{1}{2}}^{el}$ (min)	259.0 (36.5) [219.6–313.0]	309.3 (53.1)* [236.9–372.9]	266.4 (46.5) [224.1–383.9]	ns
MRT (min)	226.8 (18.1) [201.2–242.0]	284.9 (50.0)* [236.9–372.0]	277.5 (81.4) [151.2–407.7]	ns
Cl_P (ml min^{-1})	187.4 (49.5) [125.2–269.5]	158.8 (40.1)† [100.0–220.7]	114.8 (46.5)* [68.8–213.4]	< 0.02
V^{ss} (litre)	42.1 (9.7) [30.3–58.6]	44.6 (8.4)† [31.3–55.1]	30.3 (11.6) [16.1–49.7]	< 0.025
Free drug				
Cl_P (ml min^{-1})	1829 (623) [842–2717]	1089 (306) [701–1600]	869 (341)* [348–1584]	< 0.01
V^{ss} (litre)	408.8 (126) [203.7–590.6]	308.4 (74)* [175.4–370.8]	228.6 (93)* [126.8–420.4]	< 0.01

cant difference between the two liver dysfunction groups in V^{ss} ($P \leqslant 0.05$) (table II).

Alfentanil binding to plasma proteins was reduced also in the alcoholic group compared with controls ($P < 0.05$). As a result, free drug clearance was reduced significantly in the non-alcoholic group compared with control subjects ($P < 0.05$); there were also decreases in the $V^{ss}u$ in both liver dysfunction groups ($P < 0.05$ non-alcoholic group *vs* controls; $P < 0.05$ alcoholic group *vs* controls). There were no differences in the serum albumin concentration between the three groups; however, AAG concentration was significantly reduced in the alcoholic group ($P < 0.05$ *vs* controls).

There was no significant correlation within the liver dysfunction patients between total or free drug clearance and any of the biochemical variables.

DISCUSSION

The liver is one of the main sites of drug metabolism. In the presence of liver dysfunction, alterations in drug clearance may be expected. However, there are several different and separate factors that interplay with each other: liver flood flow, liver microsomal enzyme activity and protein and tissue binding of drugs [9]. Thus the increased free fraction in liver dysfunction may counterbalance the decrease in mixed function oxygenase activity. Our present data indicate that alterations in drug disposition and elimination in patients with hepatic disease may be dependent (at least in part) on the aetiology of the liver dysfunction.

In cirrhosis, there is usually marked fibrosis and nodular regeneration, resulting in circulatory changes of importance to the handling of drugs (e.g. porto–systemic intra- and extrahepatic shunting; increased plasma volume; increased cardiac output; peripheral pooling of blood; hypoalbuminaemia). Acute viral hepatitis and alcoholic liver disease have predominant effects on the pericentral regions of the hepatic lobules and are more likely, therefore, to be associated with impairment of oxidative metabolism. In contrast, chronic active hepatitis and primary biliary cirrhosis affect mainly the periportal regions, and have little effect on drug metabolism [10]. This is borne out by clearance values similar to the control group in patients with chronic active hepatitis and primary biliary cirrhosis, and reduced in patients with alcohol-related liver disease and portal venous thrombosis.

The enzymes involved in glucuronide conjugation are located throughout the liver parenchyma, with the greatest concentrations in the periportal region. Preservation of glucuronidation in chronic liver disease has been attributed to three findings: the large reserve in glucuronide transferase enzyme activity; the more protected locale of the enzymes; and extrahepatic metabolism [11].

The clearance and apparent volume of distribution estimates for the control patients are comparable to those reported in other anaesthetized patients undergoing artificial ventilation of the lungs, in whom blood sampling has been continued for > 10 h after dosing [2, 12]. Such sampling regimens identify a longer estimate for the elimination half-life and smaller clearance values than are reported in studies using shorter sampling periods.

This study and that by Ferrier and colleagues [2] have shown that liver dysfunction causes greater alterations in alfentanil disposition than has been reported previously for its congeners, fentanyl and sufentanil [13, 14]. Both the latter studies reported no effect of liver disease (mainly alcohol-related cirrhosis) on drug elimination half-life and plasma clearance. The reduced binding of alfentanil in patients with alcoholic liver disease is in agreement with the data of Ferrier's group [2] and is primarily the result of the change in plasma AAG concentrations [3]. In the latter regard, our data are at variance with those of Ferrier and co-workers, who found differences in AAG concentrations. This suggests that in our alcoholic group the degree of liver dysfunction was greater, with impaired biosynthetic activity of AAG. Greater free drug concentrations coupled with a decrease in systemic drug clearance in patients with hepatic dysfunction may result in enhanced or prolonged effects of the opioid when administered in large bolus doses, or by multiple increments or continuous infusion.

Cirrhosis influences the clearance of many i.v. drugs administered during anaesthesia. However, the effect is not uniform, thus the clearance of morphine has been reported as being both unaltered and reduced [15, 16], while that of sufentanil is apparently unaffected [14]. Yet both drugs exhibited flow-dependent clearances. A study by Colli and colleagues has compared the effects of cirrhosis on the disposition of the flow-limited drug lignocaine and the capacity-limited drug theophylline in the same individuals [17]. There was a high correlation of the degrees of impairment of both theophylline and lignocaine clearances, but only the decrease in lignocaine clearance correlated closely with the severity of the liver disease (as classified by the Child's Classification). This is further evidence for the non-uniformity of the effects of disease processes on drug handling in the body.

In summary, this study has compared the influence of different types of liver dysfunction on alfentanil disposition. Reduction in clearance appeared to be dependent only partly on the aetiology of the disease process. Our data (and those of Ferrier and colleagues [2]) indicate wide interindividual variability in alfentanil kinetics. The decrease in clearance in patients with liver disease is in contrast with the unaltered disposition of both fentanyl and sufentanil. Thus the latter opioids may provide a more predictable effect when used as part of a balanced anaesthetic technique in patients with hepatic impairment.

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EFFICACY OF ORALLY ADMINISTERED ONDANSETRON IN THE PREVENTION OF POSTOPERATIVE NAUSEA AND VOMITING: A DOSE RANGING STUDY

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SUMMARY

In a placebo-controlled, double-blind study, we have compared the efficacy of ondansetron 16 mg, 8 mg and 1 mg administered 8-hourly for prevention of postoperative nausea and vomiting. We studied 995 patients undergoing major gynaecological surgery; 982 were included in the analysis. Study medication was administered 1 h before induction of anaesthesia and second and third doses were given 8 and 16 h after the first. The treatment groups were similar for patient characteristics, surgical procedures, anaesthetics administered and opioids given. The frequency of nausea was 75%, 70%, 56% and 55% after placebo and ondansetron 1 mg, 8 mg and 16 mg, respectively; the corrresponding frequencies of vomiting were 60%, 55%, 37% and 37%. Ondansetron 8 mg was as effective as 16 mg and both resulted in significant reductions in nausea and vomiting compared with placebo and ondansetron 1 mg ($P < 0.001$*).*

KEY WORDS

Antagonists, 5-hydroxytryptamine: ondansetron. Surgery: gynaecological. Vomiting: postoperative.

Postoperative nausea and vomiting are distressing and frequent adverse events after general anaesthesia and surgery [1]. Patients who undergo gynaecological surgery may be especially at risk, with 60% experiencing emetic effects [2]. Ondansetron is a 5-hydroxytryptamine (5-HT) antagonist with selectivity for 5-HT_3 receptors [3]; it has been reported to be effective in the treatment of emesis in patients receiving cytotoxic drugs and radiotherapy [4, 5]. In addition, it has been reported recently that it was effective in the prevention of postoperative nausea and vomiting [6]. The effectiveness of various doses of ondansetron in the prevention of chemotherapy-induced emesis has been reviewed extensively [7, 8].

The present study was undertaken to compare the efficacy of ondansetron 16 mg, 8 mg and 1 mg administered 8-hourly in the prevention of postoperative nausea and vomiting. The 8-hourly doses of ondansetron 8 mg and 16 mg chosen for this study were based on the recommended oral dose for cancer chemotherapy and radiotherapy pertaining at the time. Ondansetron 1 mg three times daily was selected as a minimally effective dose [7, 8].

PATIENTS AND METHODS

This international, placebo-controlled double-blind study was carried out in 31 hospitals in the U.K., The Netherlands, Germany and Norway and was conducted with the approval of the Ethics Committees of those hospitals involved in the study. The study was explained to each patient and written informed consent was obtained. We studied patients aged 18–65 yr and weighing 45–90 kg, undergoing gynaecological surgery requiring a laparotomy or vaginal hysterectomy under general anaesthesia. Patients who were classed as ASA IV or V or who had vomited during the 24 h before administration of the study drug were excluded, as were patients who were pregnant or breast feeding. Additional exclusions included the use of antiemetics in the 24 h preceding administration of the study drug and the use of intragastric tubes after operation. Patients were allocated randomly to treatment with orally administered ondansetron 16 mg, 8 mg or 1 mg or matching placebo. The first dose of the study medication was administered approximately 1 h before induction of anaesthesia and the second and third identical doses 8 and 16 h after the first.

Premedication was administered to more than 98% of patients and all received diazepam or temazepam, apart from one patient in the placebo group who received lorazepam. The premedication was administered together with the study medication. Anaesthesia was induced using thiopentone

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TABLE I. *Patient characteristics* (*mean* (*range or* SD))

		Ondansetron		
	Placebo ($n = 249$)	1 mg ($n = 241$)	8 mg ($n = 245$)	16 mg ($n = 247$)
Age (yr)	41.6 (20–67)	41.9 (21–66)	41.9 (18–64)	43.3 (18–65)
Weight (kg)	65.4 (9.7)	65.7 (9.6)	65.8 (10.6)	66.8 (10.8)

except for four patients in the ondansetron 8 mg group, three of whom received etomidate and one who received propofol. Neuromuscular blocking agents were used as required. If necessary, atropine and neostigmine were given to antagonize neuromuscular block, although a small proportion of patients in each treatment group received glycopyrronium. Anaesthesia was maintained with nitrous oxide in oxygen supplemented with enflurane or isoflurane as required, although five patients received halothane and one had anaesthesia maintained with midazolam after failure of the anaesthetic machine. More than 96% of patients received fentanyl for intraoperative analgesia. Two patients received morphine in place of fentanyl. The duration of anaesthetic administration and the time to recovery from anaesthesia were noted. Patients were considered to have recovered from anaesthesia when they obeyed spoken commands. Postoperative analgesia was provided with morphine as necessary and prochlorperazine or metoclopramide was used as rescue antiemetic treatment if required.

The major measure of efficacy was the number of patients who did not report nausea or vomiting during the first 24 h after recovery from anaesthesia compared with those who did. Requirement for rescue antiemetic medication was considered to be a treatment failure and those patients were scored as experiencing nausea and to have vomited. Data concerning nausea and vomiting were collected by direct questioning of the patient at 1, 4 and 24 h after recovery from anaesthesia. All observations were made without knowledge of which treatment the patient received. The frequencies of nausea and vomiting were noted, together with the grade of the worst nausea experienced within the 24-h period, using the grading system: no nausea = 0; mild nausea = 1; moderate = 2; severe nausea = 3. The number of episodes of vomiting and the time to onset of the first episode were recorded. Retching was not assessed as a separate entity.

Heart rate and arterial pressures were recorded immediately before administration of the study drug, at induction, during anaesthesia and recovery and 24 h after recovery from anaesthesia. Patients were questioned about any possible side effects of the study medication at 24 h after recovery from anaesthesia and again after 5–7 days, when blood and urine samples were obtained for laboratory screening before discharge of the patient. Laboratory tests included measurement of serum concentrations of sodium, potassium, calcium, total protein, albumin, urea, creatinine, bilirubin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase and gamma-glutamyl transpeptidase. Blood samples were obtained for measurement of haemoglobin content, red blood cell count, PCV, mean cell volume, platelet count and total and differential white cell counts. Urine was analysed for the presence of protein and glucose.

Assuming a frequency of nausea and vomiting of 60% in the placebo group, the number of patients was selected to detect a 15% difference between the treatment groups at the 5% significance level with 80% power. Statistical analysis was performed on an Olivetti M380 using SAS version 6.04 (SAS Institute, Cary, NC, U.S.A.). Comparison of the frequencies and relative risks of nausea and vomiting and nausea grade were made using logistic regression techniques. The number of episodes of vomiting and the time to onset of the first episode of vomiting were compared using Wilcoxon rank sum tests, as was the time to recovery from anaesthesia. The differences in heart rates and arterial pressures between the preoperative value and the values recorded at induction, during anaesthesia, during recovery and at 24 h after recovery from anaesthesia were compared using analysis of variance techniques.

RESULTS

A total of 995 patients were entered into the study; 982 were evaluated for efficacy. Of the 13 patients who were not evaluated for efficacy, six had scheduled operations cancelled, four received antiemetics prophylactically or during the 24 h immediately preceding administration of the study drug, one patient had an intragastric tube *in situ* after operation, one patient was transferred to the intensive care unit after operation and one was withdrawn after a change in the planned operation resulted in her being extremely distressed after operation. The mean age and weight in each of the treatment groups were not significantly different (table I). Two older patients, one aged 66 yr and one aged 67 yr, were recruited, and both were included in the analysis. Five patients exceeded the recommended weight range by less than 5 kg and all were included in the analysis. There were no differences between the four groups for the mean doses or the numbers of patients who received temazepam or diazepam premedication.

The groups were well matched for types of operation performed (table II). A few patients in each group underwent either non-gynaecological surgery via laparotomy or laparoscopy, or unspecified gynaecological surgery, but all were included in the analysis of efficacy. The treatment groups were comparable in terms of the agents used for induction and maintenance of anaesthesia. Each of the treatment groups received similar amounts of opioid analgesia both during and after operation

TABLE II. *Types of operation performed*

		Ondansetron		
	Placebo ($n = 249$)	1 mg ($n = 241$)	8 mg ($n = 245$)	16 mg ($n = 247$)
Abdominal hysterectomy	153	158	135	156
Vaginal hysterectomy	37	27	41	40
Gynaecological laparotomy	50	52	61	48
Other	9	4	8	3

(table III). The duration of anaesthesia was similar for each of the groups and there were no significant differences in the times to recovery after anaesthesia (table IV).

There were significant differences between the treatment groups in the frequencies of nausea during the 24-h period after recovery from anaesthesia (table V). Ondansetron 8 mg and 16 mg resulted in a significant reduction in the frequency of nausea compared with both the 1-mg dose ($P = 0.001$) and placebo ($P < 0.001$). There was no statistical difference between ondansetron 8 mg and 16 mg or between the 1-mg dose and placebo.

The worst nausea grades experienced over the 24 h after recovery from anaesthesia in the placebo, ondansetron 1 mg, 8 mg and 16 mg treatment groups were 1.6, 1.4, 1.1 and 1.0 (mean) and 2, 1, 1 and 1 (median), respectively. Both ondansetron 8 mg and 16 mg significantly decreased the worst nausea grade compared with the 1-mg dose and placebo (8 mg *vs* 1 mg: $P = 0.005$; 16 mg *vs* 1 mg: $P = 0.001$; 8 mg and 16 mg *vs* placebo: $P < 0.001$). There were no significant differences between the 8-mg and 16-mg doses or between the 1-mg dose and placebo.

There was a significant reduction in the number of patients who experienced vomiting during the first 24-h period after recovery from anaesthesia for those treated with ondansetron 8 mg and 16 mg compared with patients who received 1 mg ($P < 0.001$) or placebo ($P < 0.001$) (table V). There were no significant differences between ondansetron 8 mg and 16 mg or between the 1-mg dose and placebo.

The median times to the first episode of vomiting were significantly longer for patients who received ondansetron 8 mg and 16 mg compared with those given the 1-mg dose and placebo ($P < 0.001$ for all comparisons) (table VI). There were no significant differences between the 8-mg and 16-mg doses or between the 1-mg dose and placebo.

TABLE IV. *Duration and recovery from anaesthesia (median (range))*

		Ondansetron		
	Placebo ($n = 249$)	1 mg ($n = 241$)	8 mg ($n = 245$)	16 mg ($n = 247$)
Anaesthetic duration (min)	85 (35–297)	90 (26–257)	90 (32–276)	95 (20–272)
Recovery time (min)	7 (0–60)	7 (0–85)	7 (0–185)	8 (0–155)

TABLE V. *Percentages of patients in each treatment group who experienced nausea or vomiting in the first 24 h after recovery from anaesthesia*

		Ondansetron		
	Placebo ($n = 247$)	1 mg ($n = 238$)	8 mg ($n = 243$)	16 mg ($n = 245$)
Patients experiencing nausea (%)	75	70	56	55
Patients experiencing vomiting (%)	60	55	37	37

TABLE VI. *Median time to first episode of vomiting (h) (data unadjusted for rescue antiemetics)*

		Ondansetron		
	Placebo	1 mg	8 mg	16 mg
Patients who vomited	3.5	4.0	5.4	6.5
n	133	117	81	76
All patients	15.8	> 24.0	> 24.0	> 24.0
n	247	238	243	245

Both ondansetron 8 mg and 16 mg resulted in significant reductions in the number of episodes of vomiting compared with the 1-mg dose and placebo ($P < 0.001$ for all comparisons) (table VII). There were no significant differences between the 8-mg and 16-mg doses or between the 1-mg dose and placebo.

When the relative risks of experiencing nausea and vomiting were calculated, patients were found to be approximately 40% as likely to experience these symptoms after ondansetron 8 mg or 16 mg treatment as after placebo (table VIII).

TABLE III. *Opioid analgesics used during and after operation (mean (range))*

		Ondansetron		
Opioid administered	Placebo ($n = 249$)	1 mg ($n = 241$)	8 mg ($n = 245$)	16 mg ($n = 247$)
During operation				
Fentanyl (μg)	302 (25–800)	315 (25–800)	313 (10–750)	309 (25–650)
n	243	236	242	242
After operation (0–24 h)				
Morphine mean dose per patient (mg)	39.8	40.1	38.9	39.5
n	244	234	234	243

TABLE VII. *Number of episodes of vomiting (data unadjusted for rescue antiemetics)*

		Ondansetron		
	Placebo ($n = 247$)	1 mg ($n = 238$)	8 mg ($n = 243$)	16 mg ($n = 245$)
No. patients who vomited	133	177	81	76
No. episodes				
Mean	1.6	1.6	0.9	0.9
Median	1	0	0	0
Range	0–13	0–20	0–10	0–10

Side effects were recorded for all patients, regardless of possible cause. The frequency of reporting was similar for all groups (36 % of patients in the placebo group and 37 % of patients who received ondansetron). The majority of side effects reported were those that might be expected in surgical patients and there were no important differences between treatment groups. Increases in aminotransferase activities (ALT and AST) to greater than the reference ranges were common in all treatment groups, with a slightly greater incidence in patients treated with ondansetron (ALT 19 %; AST 17 %) compared with placebo (ALT 14 %; AST 15 %).

There were no significant differences in heart rates or diastolic arterial pressures between the groups. There were increases in systolic pressure during the period between induction and recovery and during the period immediately following recovery in the ondansetron 16 mg group compared with the placebo group. The treatment difference was statistically significant, but did not exceed 5 mm Hg.

DISCUSSION

This study was designed to identify the optimum dose and side effects of ondansetron 1 mg, 8 mg and 16 mg given orally three times a day, for prevention of postoperative nausea and vomiting after gynaecological surgery. The treatment groups were similar in terms of the type of patient and their characteristics, surgical procedure, types of anaesthetics used and opioid analgesics administered. The frequencies of nausea (75 %) and vomiting (60 %) observed in the placebo group were comparable to those reported previously [2]. Ondansetron reduced the frequency of nausea and vomiting in a dose-dependent manner compared with placebo and was equally effective against both symptoms. Not only was the frequency of nausea decreased but, in addition, the severity of nausea experienced was reduced as assessed by the worst nausea grade recorded for each patient. The 8-mg and 16-mg doses consistently provided significant improvement compared with the 1-mg dose, but there were no significant differences in efficacy between placebo and the 1-mg dose or between the 8-mg and 16-mg doses.

There were no significant differences in the overall frequency of side effects with ondansetron compared with placebo. Transient asymptomatic increases in alanine and aspartate aminotransferase activities were common in the placebo group. There were small increases in transaminase activities in the ondansetron-treated patients compared with the placebo treatment group, but the differences were unlikely to be of clinical significance. Asymptomatic increases in transaminases have been reported during the use of ondansetron for the treatment of nausea and vomiting during cytotoxic therapy and are included in existing prescribing information for this indication.

The increase in systolic arterial pressure after treatment with ondansetron 16 mg was of small magnitude and had no clinical relevance in the population studied. It remains to be investigated if this effect is more evident in patients who suffer from pre-existing hypertension. No other significant effects were observed on the cardiovascular system.

There was no effect of ondansetron on recovery time after anaesthesia. This is an important consideration for the treatment of patients undergoing day-case surgery, in whom major requirements are a rapid recovery from anaesthesia followed by minimal postoperative nausea and vomiting.

In conclusion, we found that three doses of ondansetron administered orally at 8-hourly intervals significantly reduced the frequency and severity of postoperative nausea and the frequency and number of episodes of vomiting. Both ondansetron 8 mg and 16 mg were more effective than 1 mg and placebo. An earlier study [6] has reported the efficacy of ondansetron 16 mg, administered orally 1 h before anaesthesia and again 8 h later, in preventing postoperative nausea and vomiting. The present study suggests that ondansetron 16 mg is no more effective than 8 mg when given three times a day. Ondansetron appeared to be well tolerated and effective in the prevention of postoperative nausea and vomiting.

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TABLE VIII. *Relative risk (95 % confidence interval) of experiencing nausea or vomiting during the first 24 h after recovery from anaesthesia for ondansetron compared with placebo*

	Ondansetron 1 mg	Ondansetron 8 mg	Ondansetron 16 mg
Nausea	0.77 (0.52–1.15)	0.42 (0.29–0.61)	0.40 (0.28–0.59)
Vomiting	0.82 (0.57–1.17)	0.40 (0.28–0.58)	0.40 (0.28–0.58)

We wish also to thank Ms J. M. Durham for expert statistical analysis, Mr I. Jeffreys for data management and Dr A. E. Duggan for her work in co-ordinating the trial.

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RELATIONSHIP BETWEEN HYPOXAEMIC AND CARDIAC ISCHAEMIC EVENTS IN THE PERIOPERATIVE PERIOD

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SUMMARY

We have used continuous and concurrent monitoring of arterial oxygen saturation (Sp_{O_2}) and ECG to study the relationship between hypoxaemia and silent myocardial ischaemia in the perioperative period in 11 patients with cardiovascular disease. Ischaemic and hypoxaemic events occurred in all patients. Many events were shortlived and occurred independently of each other. However, our results suggest a close correlation between the duration of hypoxaemia and myocardial ischaemia. Ischaemia is more likely to occur if an episode of hypoxaemia is prolonged (beyond 5 min; $P < 0.01$, chi square) and severe ($Sp_{O_2} < 85\%$; $P < 0.05$, chi square).

KEY WORDS

Heart: myocardial ischaemia. Hypoxia: perioperative. Monitoring: pulse oximetry.

Patients with cardiovascular disease are at risk of developing myocardial ischaemia in the perioperative period [1]. Silent ischaemia may occur in up to 86 % of such patients after operation [2]. These events may be associated with significant morbidity and mortality [3, 4].

Episodes of hypoxaemia are common in the postoperative period [5] and may increase the risk of ischaemia developing. Causes of hypoxaemia include hypoventilation secondary to pain, central respiratory depression or upper airway obstruction. Episodes of severe desaturation may also occur before operation [6] and these may be related to respiratory depression or apnoea during sleep, especially rapid eye movement sleep.

The aim of this study was to assess the temporal relationship between perioperative ischaemic and hypoxaemic events in patients with cardiovascular disease, by continuous and concurrent monitoring of arterial oxygen saturation (Sp_{O_2}) and ECG.

PATIENTS AND METHODS

After obtaining Ethics Committee approval and written informed consent, we studied 11 patients (age range 58–80 yr; seven male) undergoing elective general or urological surgery. All were known to have cardiovascular disease before operation. This included a history of angina, previous myocardial infarction (> 6 months before), treated hypertension, or a combination of these conditions.

Each patient underwent simultaneous and continuous monitoring of ECG and Sp_{O_2} with a pulse oximeter. Monitoring was commenced before operation either the night before, or morning of, surgery, discontinued during surgery itself and then recommenced after operation in the recovery ward. After operation, all patients were prescribed oxygen 4 litre min^{-1} via a face mask overnight.

The ECG was recorded continuously using a Compas ambulatory monitor. This type of monitor has been described in previous studies [2]. In this study it was programmed to an ST mode selecting augmented leads V2, V5 and AvF. The ST mode reported changes in the ST segment lasting > 30 s and included ST elevation > 2 mm or depression > 1 mm. The times at which these changes started and ended were recorded.

In this study we defined an ischaemic event as a period of ST segment depression of > 1 mm or elevation of > 2 mm lasting for 1 min or more.

Sp_{O_2} was measured using an Ohmeda 3700 pulse oximeter with a finger probe which was connected to a BBC Master computer programmed to record to disc the Sp_{O_2} every 6 s when it decreased to less than 90 %.

We defined a hypoxaemic event as an incident of $Sp_{O_2} < 90\%$ for at least 30 s.

The internal clocks of the Compas monitor and the BBC computer were synchronized at the start of each study. Data from the two monitors were downloaded at the end of the preoperative monitoring period and on the 1st and 2nd days after operation.

For each ischaemic event, its duration, the mean and least Sp_{O_2} during the 2 min before the start of the event and the mean Sp_{O_2} during the 2 min after the event were recorded. Heart rates at beginning and end of each event were noted.

For each hypoxaemic event we recorded its duration, the smallest Sp_{O_2} and whether or not ischaemia occurred during the event.

For each 1 h of monitoring the total hypoxaemic time and the total ischaemic time were calculated.

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Statistical analyses were performed using SPSS/PC+V2.0. Chi square was used to examine associations between ischaemic and hypoxaemic events. Comparisons of means were performed using ANOVA. Other associations were sought using correlations.

RESULTS

Monitoring was conducted for a mean time of 13.8 h (range 7.6–19.9 h) before operation and 32.3 h (range 11–46 h) after operation. Hypoxaemic events occurred in nine patients before operation and in 10 after operation. Ischaemic events occurred in seven patients before operation and in nine after operation.

There were 278 hypoxaemic events (86 before operation, 191 after operation) with a mean duration of 7.6 min (range 0.5–493 min). Postoperative events had a mean duration of 9.6 min, significantly longer than the preoperative value of 2.7 min ($P < 0.05$, ANOVA). The mean least Sp_{O_2} recorded was 84 % (range 63–89 %) and this was the same before and after operation. Ischaemia occurred in 65 events (23 %).

There were 237 ischaemic events (72 before operation, 165 after operation), with a mean duration of 11.5 min (range 0.5–902 min). There was no significant difference between the duration of events before and after operation. Hypoxaemia was recorded during 41 events (17 %); 24 (10.1 %) were preceded and 26 (11 %) were followed by a mean $Sp_{O_2} < 90$ %.

When the ischaemic events were grouped according to duration, and whether or not there was concurrent hypoxaemia (table I), a significantly greater proportion of events lasting 5 min or more were associated with hypoxaemia ($P < 0.001$, chi square). When postoperative events alone were examined, the same association occurred.

TABLE I. *Duration of ischaemic events* (n) *associated with desaturation. Significant differences between groups* ($P < 0.001$, *chi square*)

Duration	No desaturation	Desaturation
< 5 min	157	15
> 5 min	39	26

TABLE II. *Duration of desaturation events* (n) *associated with ischaemia. Significant differences between groups* ($P < 0.01$, *chi square*)

Duration	No ischaemia	Ischaemia
< 5 min	165	35
> 5 min	48	30

TABLE III. *Minimum saturation* (Sp_{O_2}) *achieved during desaturation events* (n) *associated with ischaemia. Significant differences between groups* ($P < 0.05$, *chi square*)

Minimum Sp_{O_2} (%)	No ischaemia	Ischaemia
85–90	137	32
< 85	76	33

A similar analysis of hypoxaemic events with grouping according to duration and whether or not there was concurrent ischaemia (table II) demonstrated that a significantly greater proportion of events lasting 5 min or more were associated with ischaemia ($P < 0.01$, chi square). The same association occurred with postoperative events alone.

The mean duration of hypoxaemic events with ischaemia was 14.4 min (range 0.5–493 min, median 4 min), whereas that of those events without ischaemia was 5.5 min (range 0.5–88 min; median 1.5 min). This difference was significant ($P < 0.05$, ANOVA).

Analysis of the hypoxaemic events by the least Sp_{O_2} recorded, and whether or not ischaemia occurred (table III) showed that a significantly larger proportion of events in which Sp_{O_2} decreased to less than 85 % was associated with ischaemia than with Sp_{O_2} 85 % or greater ($P < 0.05$, chi square). When postoperative events alone were analysed, this association was not significant ($P = 0.08$).

The hourly ischaemic time had a significant positive correlation with the hourly hypoxaemic time ($P < 0.001$). There was a significant negative correlation between the duration of an ischaemic event and the least Sp_{O_2} recorded during that event ($P < 0.001$). There was a significant negative correlation between the duration of an hypoxaemic event and the least Sp_{O_2} recorded during that event ($P < 0.01$), but no correlation between the administration of oxygen therapy and the duration or severity of a hypoxaemic event.

There was no correlation between the duration of an ischaemic event and the heart rate at either beginning or end of the event.

DISCUSSION

Previous studies have demonstrated a high incidence of both ischaemic and hypoxaemic events in the perioperative period [2, 6, 7]. The relationship between episodic hypoxaemia and postoperative myocardial infarction is unclear and is a subject of considerable interest [8]. The study by Rosenberg and colleagues suggested that hypoxaemia and tachycardia may be involved in the development of late postoperative ischaemia in patients without cardiovascular disease [7].

In our study, episodes of myocardial ischaemia and hypoxaemia occurred in all our patients at some time during the perioperative period. The majority of these events were shortlived, lasting less than 5 min, and appeared to occur independently of each other. However, the episodes of hypoxaemia during which ischaemia occurred were significantly longer in duration (5 min or more) and more severe (Sp_{O_2} < 85 %) than those episodes during which ischaemia did not occur. Similarly, the duration of episodes of ischaemia associated with hypoxaemia were significantly longer than those events during which hypoxaemia did not occur. The close correlation between the overall hourly ischaemic and hypoxaemic times emphasizes the relationship between hypoxaemia and ischaemia. Whereas the severity of hypoxaemic events as judged by least recorded Sp_{O_2}

was not significantly different before and after operation, the duration of events was. As the association between ischaemia and severity of hypoxaemia is weaker in the postoperative period, it may be that the duration of hypoxaemia is the more important factor implicated in the development of ischaemia.

The significance of perioperative silent ischaemia and its relationship to patient morbidity and mortality is not well established, but some studies have shown a correlation with adverse postoperative cardiac events in patients undergoing coronary artery bypass grafting [3] or non-cardiac vascular surgery [4]. The pathogenesis of transient ischaemic events may be related to decreases in oxygen supply rather than increased demand, resulting from increased coronary artery tone or platelet aggregation [9]. Such factors may be responsible for many of the shorter episodes of ischaemia we recorded which were not associated with a decrease in Sp_{O_2}. However, where the physiological insult of hypoxaemia is added to an already compromised coronary circulation, it would seem likely that a more significant period of ischaemia could result. Our data support this concept, and suggest that there is a close relationship between hypoxaemia and ischaemia in the perioperative period.

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I.V. DICLOFENAC IN POST-THORACOTOMY PAIN

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SUMMARY

We have studied the efficacy of a continuous i.v. infusion of diclofenac 2 mg $kg^{-1}/24$ h given for 2 days after major thoracic surgery in 30 patients in a double-blind, placebo-controlled, parallel-group design. The patients were able to obtain additional pain relief as on demand morphine boluses. In the diclofenac group, the consumption of morphine was reduced by 60% during the first and by 76% during the second day after operation compared with the control group. Overall, analgesia was also superior in the diclofenac group. Arterial oxygenation was significantly greater and the arterial P_{CO_2} increased less during the first day after operation in the diclofenac group compared with the control group. Diclofenac had no significant effect compared with placebo on blood loss or on any bleeding or platelet test. Urine output was significantly less during the first day after operation in the diclofenac group compared with the control group, but was normal on the second day after operation; plasma creatinine concentrations were unchanged. I.v. diclofenac infusion combined with opioids delivered via a patient-controlled analgesia device seems a valuable method of pain relief after thoracic surgery in patients in whom more invasive techniques, such as extradural local anaesthetics and opioids, cannot be used. However, non-steroidal anti-inflammatory drugs should be used cautiously, if at all, in patients who are at risk of acute renal failure.

KEY WORDS

Analgesics non-steroidal: diclofenac. Pain: postoperative. Surgery: thoracotomy.

Adequate pain treatment after thoracic surgery requires greater doses of opioids than after orthopaedic or lower abdominal surgery [1]. However, post-thoracotomy pain seems to be more responsive to opioids than pain after upper abdominal surgery [1]. Good pain treatment is essential to ensure adequate breathing, but there is always concern about the potential for respiratory depression, therefore other methods of pain relief have been used [2]. The most effective methods, such as continuous extradural infusion of opioids and local anaesthetics, usually require monitoring in high dependency units.

Various studies have shown that non-steroidal anti-inflammatory drugs (NSAID) are effective in reducing pain after orthopaedic surgery [3, 4], whereas the results of their efficacy in the treatment of pain after upper abdominal surgery are more controversial [5, 6]. Qualitatively, post-thoracotomy pain would be expected to resemble more closely the pain after orthopaedic surgery than that after abdominal surgery and therefore should respond to NSAID. Indeed, this has been shown to be the case with lysine acetyl salicylate [7] and in a recent study with indomethacin [8]. NSAID do not cause respiratory depression, but other side effects have been reported, including increased bleeding time, gastrointestinal symptoms, central nervous system symptoms and depression of renal function.

Diclofenac is the sodium salt of aminophenylacetic acid. It was developed as an analgesic, but also has anti-inflammatory and antipyretic properties [9]. It has a plasma half-life of about 1–2 h [10]. Currently in Finland, diclofenac has a product licence for i.v. use only.

Our aim was to study the effects of a continuous 48-h infusion of diclofenac on the consumption of morphine and the quality of pain relief after thoracic surgery. Special attention was paid to possible side effects, and therefore thrombocyte function, urine output and respiratory variables were measured.

PATIENTS AND METHODS

Patients

Approval was obtained from the Institutional Ethics Committee for this double-blind, 2-day infusion, parallel-group study on 30 patients undergoing elective thoracotomy at the Helsinki University Central Hospital. Informed consent was obtained from each patient before surgery.

We studied ASA I–III patients younger than 75 yr. Patients with clinically manifest cardiac, renal or hepatic failure were excluded, as were patients with a history of gastrointestinal bleeding or peptic ulceration, haemorrhagic diathesis and asthma or allergy to acetylsalicylic acid or diclofenac. Confused patients and those with an estimated postoperative FEV_1 less than 1.0 litre s^{-1} were excluded also.

Anaesthesia and surgical procedures

All patients received standard anaesthesia. Morphine 0.13 mg kg^{-1} was given i.m. as premedication about 1 h before surgery. Glycopyrronium 4 μg kg^{-1} was administered i.v. just before induction. After precurarization with pancuronium 15 μg kg^{-1}, general anaesthesia was induced with fentanyl 3 μg kg^{-1}

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and thiopentone. Suxamethonium 1.5 mg kg^{-1} was given to facilitate endobronchial intubation (Robertshaw or Bronchocath tubes). No additional opioids were given during anaesthesia, which was maintained with 50% nitrous oxide and 1–2.5% enflurane in oxygen. During one-lung ventilation the inspired oxygen concentration was increased according to arterial blood-gas analysis. Neuromuscular block was achieved with pancuronium and monitored visually using a peripheral nerve stimulator. Normoventilation was controlled by continuous monitoring of end-tidal carbon dioxide concentration and with repeated arterial blood-gas analyses at least every 30 min. At the end of the anaesthesia, residual neuromuscular block was antagonized with neostigmine 2 mg and glycopyrronium 0.4 mg i.v. Pulmonary operations were performed through a standardized thoracotomy at the 5th intercostal space. Before wound closure the surgeon performed intrathoracic intercostal nerve blocks (T3–7) with 0.5% bupivacaine.

Pain relief

The patients were allocated randomly to receive in a double-blind fashion either a diclofenac or a placebo infusion which was started immediately after the patient had arrived into the recovery room. The infusions were prepared by a recovery room nurse who was not involved in the study.

Group 1 (*Control*). The placebo infusion (0.9% sodium chloride 400 ml) was started with a bolus dose of 25 ml in 15 min and continued with a constant rate of 2 ml kg^{-1}/24 h for 48 h.

Group 2 (*Diclofenac*). The diclofenac infusion (diclofenac 400 mg in 0.9% sodium chloride 400 ml) was started with a bolus dose of 25 ml in 15 min and continued with a constant rate of 2 ml kg^{-1}/24 h for 48 h.

Both infusions were given via an infusion pump (Oximetrix Inc., Mountain View, CA.). All patients were allowed also to take supplementary doses of morphine 10 mg ml^{-1} i.v. from a patient-controlled analgesia (PCA) device (Prominject; Pharmacia AB, Sweden). The PCA device was programmed to provide a bolus dose of 3 mg given over 1 min followed by a tail dose of 2 mg (a continuous infusion of morphine in 60 min); the lock-out time was 30 min. The times of the self-administered morphine doses were recorded. If the morphine dose delivered by PCA was not sufficient for pain relief, morphine 5 mg was given i.m. The patients stayed in the recovery room for the first night after operation.

Assessment of pain and side effects

The patients were interviewed by the observer who was blinded to which infusion the patient was receiving. On the day of operation, the interview was performed at the beginning of the study infusion and every 30 min for 2 h and then at 4, 6 and 8 h. On the first and second days after operation, patients were interviewed at 08:00, 12:00, 16:00 and 20:00. They were asked to assess the intensity of wound pain at rest using a 50-cm visual analogue scale (VAS) [11]. The patients were asked also to assess the pain intensity for shoulder pain using a verbal rating scale (VRS: none = 0; mild = 1; moderate = 2; severe = 3).

On the first and second days after operation the patients were asked if they had any of the following symptoms: drowsiness, confusion, nausea, vomiting, itching, abdominal pain, dizziness, hallucinations, difficulties with breathing or allergic reactions. At the same time, they were asked to rate sleeping, moving around, drinking, eating and defaecating, using a scale of: absent (0), moderately impaired (1) or normal (2). The axillary temperature was measured before operation and on the first, second and third days after operation at 16:00.

Laboratory tests and haemostasis

Plasma creatinine concentration was measured before operation and on the first day after operation. Haemoglobin concentration and PVC were measured before operation, 2 h after operation and on the first, second and third days after operation.

Platelet count and the Ivy (forearm) bleeding time (Simplate-II; General Diagnostics, Warner-Lambert Co., Morris Plains, New Jersey) were performed (always by the same person) before operation and 2, 8, 24, 48 and 72 h after the start of the study infusion.

The platelet adhesion test (Adeplat S; Platelet Adhesion Test Set, Semmelweis S.r.l., div. Mascia Brunelli; Milano, Italy) was performed immediately before the study infusion was started and 2 h later. Platelet adhesiveness was measured with an *in vitro* technique which entails the passage of a known volume of blood through a set of glass micro-beads. The rate of blood flow through the column was kept constant by use of an infusion pump (Adeplat Pump System). All the variables which influence the retention of platelet by the glass were standardized [12].

Thromboelastography (TEG) [13, 14] (Thrombelastograph D; Hellige GMBH, Freiburg im Breisgau, Germany) was performed immediately before the study infusion was started and 2 h later, using citrated whole blood. Coagulation was initiated by adding calcium chloride to the cuvettes. TEG tracings were analysed by measuring reaction time (R, min), coagulation time (k, min), R+k (min) and maximum amplitude (MA, mm).

Blood loss through the drainage during and after operation was measured and any loss exceeding 400 ml was replaced with whole blood.

Respiratory status

Spirometry was performed before operation to permit estimation of postoperative FEV_1. A chest x-ray was taken before operation, 1 h after the operation and on the first morning after operation.

The patients breathed 28% or 35% oxygen through a Venturi mask until at least the first morning after operation. Arterial blood-gas analysis was performed before, during and after operation before the study infusion and then every 30 min for the first 2 h, and then at 2-h intervals for the next 6 h, and again on the first morning after operation.

TABLE I. *Patient characteristics and operation data (mean (range or* SEM*))*

	Diclofenac	Placebo
n	15	15
Sex (F/M)	4/11	2/13
Age (yr)	59.1 (38–75)	55.3 (23–74)
Weight (kg)	76.9 (4.1)	72.8 (4.0)
Height (cm)	174.4 (1.6)	173.9 (1.8)
ASA class (I/II/III)	3/12/0	2/10/3
Pa_{CO_2} (kPa)	5.5 (0.1)	5.3 (0.1)
Pa_{O_2} (kPa)	10.4 (0.4)	9.8 (0.3)
Benign/malignant tumour	2/13	4/11
Surgery		
Pneumectomy	1	4
Lobectomy or bilobectomy	12	5
Wedge resection	1	3
Exploration	1	3
Duration of operation (min)	122 (9)	106 (13)
Duration of anaesthesia (min)	181 (10)	163 (14)
Time from intercostal block to the study (min)	61 (4)	59 (4)
0.5 % bupivacaine used for block (ml)	16.2 (1.1)	16.4 (1.0)

Arterial oxygen partial pressure values were divided by the inspiratory oxygen fraction (Pa_{O_2}/FI_{O_2}) to allow comparison of values obtained during various methods of oxygen supplementation. Oxygen saturation was monitored continuously by pulse oximetry using a finger probe (Satlite, Datex, Instrumentarium Corp., Helsinki, Finland) until the first morning after operation.

Statistical analysis

Student's *t* test was used for comparison of the characteristics of the patient groups. A two-way analysis of variance for repeated measures and Scheffé's method for testing all contrasts were used for the statistical analysis of VRS, VAS, consumption of morphine, Pa_{O_2}/FI_{O_2}, Pa_{CO_2}, Ivy bleeding times and platelet counts, followed by Mann–Whitney *U* test at individual time points, when needed. Urine output, plasma creatinine concentration, platelet adhesion test values and blood loss were analysed with the Mann–Whitney *U* test for unpaired data and with the Wilcoxon signed rank test for paired data. The incidence of side effects was compared using the chi-square test. $P < 0.05$ was considered statistically significant. Means and SEM are presented. The statistical calculations were performed using StatView SE+Graphics version 1.03 run on Macintosh SE.

RESULTS

There were no significant differences between the groups for age, sex, height, weight, ASA class, preoperative Pa_{O_2} and Pa_{CO_2}, type or duration of surgery or anaesthesia, amount of 0.5 % bupivacaine injected and the time from the intercostal block to the start of the study (table I).

Morphine consumption and pain relief

The consumption of morphine was significantly less in the diclofenac group compared with the control group during both the first (32.4 (6.5) mg *vs* 80.4 (11.2) mg; $P = 0.002$) and the second (14.4 (3.0) mg *vs* 59.8 (6.6) mg; $P = 0.0001$) 24-h study periods. Three patients in the diclofenac group and nine patients in the control group required supplementary i.m. morphine. The consumption of morphine decreased significantly from the first to the second day after operation in the diclofenac group ($P < 0.05$), but not in the control group (fig. 1).

The patients in the control group experienced significantly more wound pain during the immediate postoperative period (up to 120 min) ($P < 0.05$) and on both mornings after operation (fig. 2) On the first

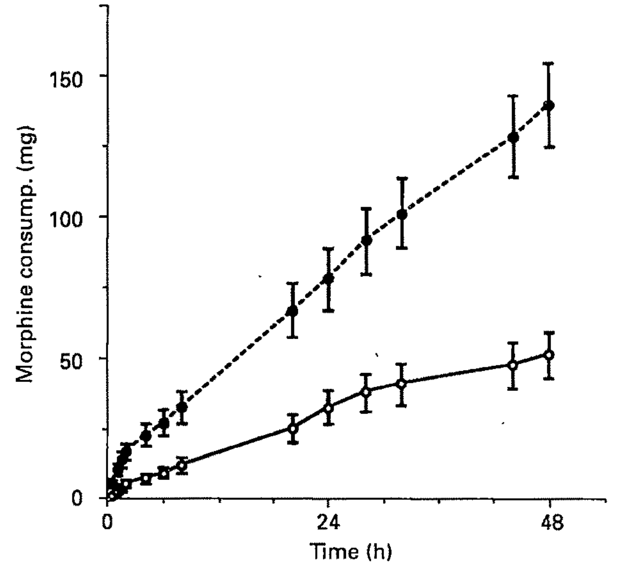

FIG. 1. Mean (SEM) cumulative consumption of morphine was significantly less ($P = 0.002$ at 24 h and $P = 0.0001$ at 48 h) in the diclofenac group (○) compared with the control group (●).

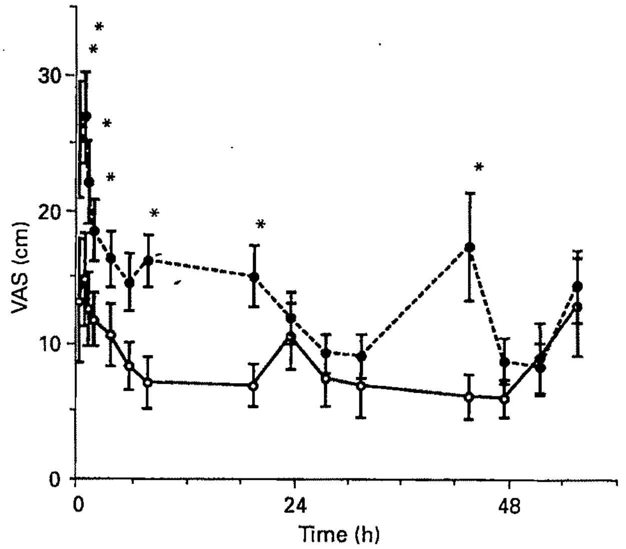

FIG. 2. Mean (SEM) visual analogue scale (VAS, 0–50 cm) values for wound pain at rest during 8 h from the start of the study and at 08:00, 12:00, 16:00 and 20:00 during the first and second days after operation. $n = 15$. * $P < 0.05$ between groups. ○ = Diclofenac; ● = control.

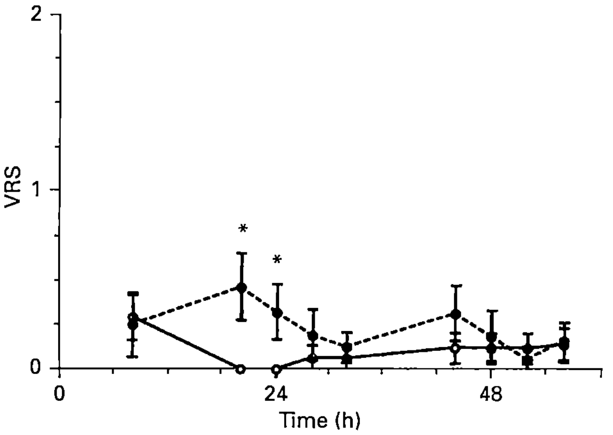

FIG. 3. Mean (SEM) verbal rating scale (VRS) values for shoulder pain at 8 h from the start of the study and at 08:00, 12:00, 16:00 and 20:00 during the first and second days after operation. $^*P < 0.05$ between groups. ○ = Diclofenac; ● = control.

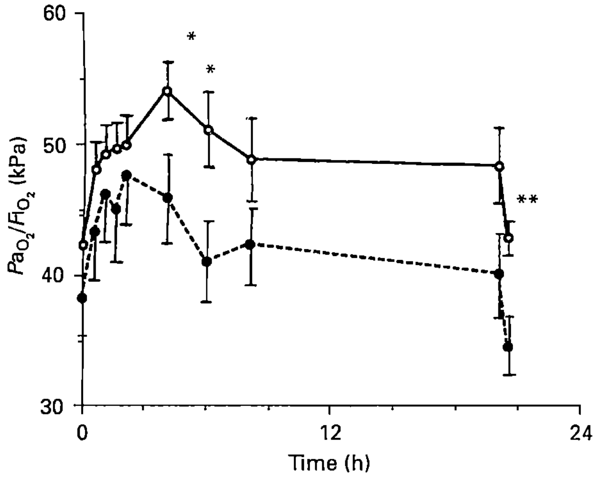

FIG. 4. Mean (SEM) Pa_{O_2}/FI_{O_2} were significantly greater in the diclofenac group (○) at 4 and 6 h ($^*P < 0.05$) from the start of the drug infusion and on the first morning after operation ($^{**}P < 0.01$). ● = Control.

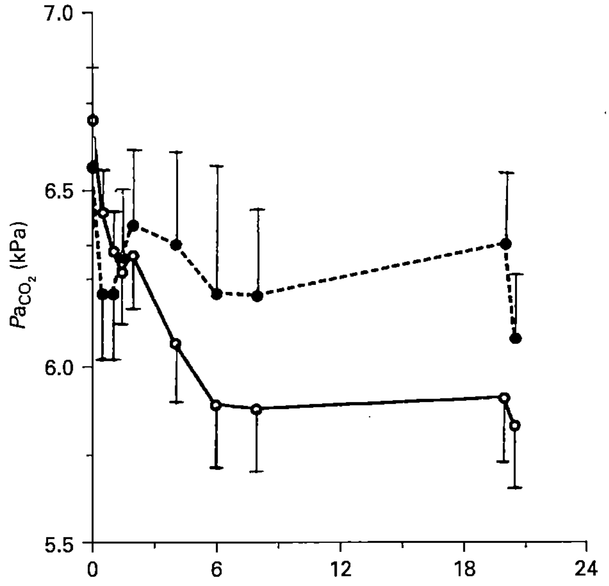

FIG. 5. Mean (SEM) Pa_{CO_2} did not differ significantly between the diclofenac (○) and control (●) groups.

morning after operation, significantly less ($P < 0.05$) shoulder pain was experienced in the diclofenac group (fig. 3).

Blood-gas analysis

Arterial oxygenation was significantly greater in the diclofenac group compared with the control group at 4, 6 and 20 h with oxygen supplementation and at 20.5 h without oxygen supplementation (fig. 4). There were no significant differences in the actual Pa_{CO_2} values between groups, but the mean increase in Pa_{CO_2} from the preoperative values to those at 20 h was significantly greater ($P < 0.05$) in the control group (20 (3.3) %) compared with the diclofenac

TABLE II. *Variables of haemostasis (mean (SEM)). Platelet adhesion test and thromboelastography : time 0 = time just before start of the study infusion. Ivy bleeding time and platelet count : time 0 = time just before anaesthesia. Blood loss : time 0 = peroperative blood loss. MA = maximum amplitude ; R = reaction time ; R+k = coagulation time. No statistically significant differences between the groups in any variable*

	Time (h)					
	0	2	8	24	48	72
Platelet adhesion (%)						
Diclofenac ($n = 11$)	99.2 (0.4)	99.5 (0.2)				
Placebo ($n = 13$)	98.7 (0.6)	98.5 (0.7)				
Thromboelastography						
Diclofenac ($n = 11$)						
MA (mm)	46 (2)	42 (3)				
R (min)	6.2 (0.6)	5.7 (0.4)				
R+k (min)	11.6 (1.0)	10.2 (0.7)				
Placebo ($n = 13$)						
MA (mm)	50 (3)	46 (3)				
R (min)	6.5 (0.7)	5.9 (0.7)				
R+k (min)	12.8 (1.4)	10.7 (1.2)				
Ivy bleeding time (min)						
Diclofenac ($n = 15$)	6.0 (0.6)	5.7 (0.3)	6.0 (0.5)	6.4 (0.6)	6.0 (0.6)	5.4 (0.6)
Placebo ($n = 15$)	5.5 (0.3)	5.3 (0.5)	5.1 (0.4)	5.4 (0.5)	5.1 (0.4)	5.2 (0.5)
Platelet count ($\times 10^3$ ml^{-1})						
Diclofenac ($n = 15$)	271 (16)	247 (16)	258 (16)	241 (16)	230 (15)	247 (16)
Placebo ($n = 15$)	317 (36)	262 (28)	280 (31)	267 (31)	248 (27)	266 (28)
Blood loss (ml)						
Diclofenac ($n = 15$)	423 (84)			480 (61)	351 (52)	
Placebo ($n = 15$)	570 (229)			535 (110)	365 (61)	

TABLE III. *Variables reflecting renal function (mean* (SEM) *and* [*range*]). n = *15 unless indicated otherwise.* *P < *0.05 compared with placebo;* **P < *0.01 compared with 2nd day*

	Diclofenac	Placebo
Creatinine (mmol litre^{-1})		
Before op.	91 (4.1) [69–119]	80 (2.5) [59–93]
After op.	87 (6.2) (n = 12) [59–126]	76 (3.3) (n = 14) [49–101]
Urine output (ml)		
1st day after op.	41 (30)* ** [0–400]	230 (77)** [0–850]
2nd day after op.	1220 (101) [700–2200]	1268 (129) [350–2050]
Crystalloid solutions given (ml kg^{-1})		
1st day after op.	33 (2)	35 (2)

TABLE IV. *Frequency of side effects on first and second days after operation (number of patients affected).* n = *15 in both groups*

	Diclofenac		Placebo	
	Day 1	Day 2	Day 1	Day 2
Drowsiness	9	7	6	4
Dizziness	6	3	4	2
Nausea	6	0	2	1
Vomiting	2	0	1	0

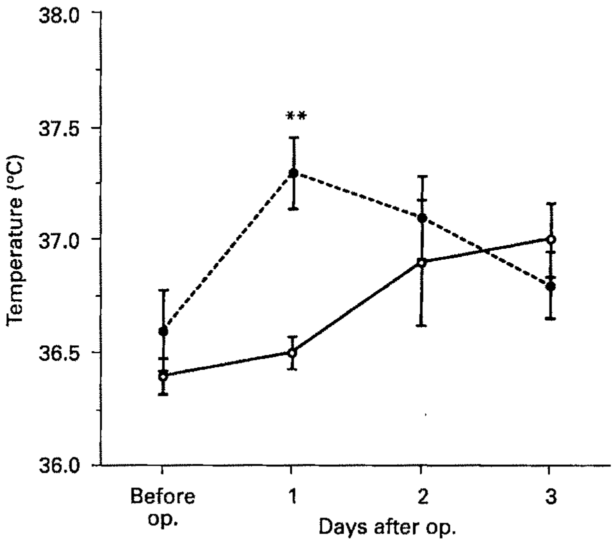

FIG. 6. Mean (SEM) axillary temperatures before operation and on three days after operation at 16:00. **$P < 0.01$ compared with diclofenac group (○). ● = Control.

group (7.5 (4.1)%) (table I, fig. 5). No atelectases were seen in any of the postoperative chest x-rays.

Haemostasis (table II)

The prestudy values of the platelet adhesion test, Ivy bleeding time, platelet count and thromboelastography variables were comparable in the two groups and did not differ significantly between or within the groups at the various time points, with the exception of the platelet count, which decreased with time in both groups. No significant difference in platelet counts was found between the groups even when the values were corrected for the changes in PCV.

Renal function (table III)

There were no significant differences between the groups in the creatinine concentrations either before or after operation. The urine output was significantly less in both groups during the first day after operation than during the second day ($P < 0.01$). The urine output during the first day after operation was significantly less ($P < 0.05$) in the diclofenac than in the control group. Thirteen patients in the diclofenac group and nine patients in the control group had a urine output less than 100 ml during the first day after operation. There were no significant differences in the amounts of crystalloids infused between the two groups.

Other side effects

There were no significant differences between the groups in the side effects (table IV). The diclofenac group had a significantly better total performance status (sum of all function scores) on the second day after operation (9.3 (0.3) *vs* 7.8 (0.5); $P < 0.05$), but no differences were found between the individual scores of the functions.

The mean axillary temperatures measured before operation and on the three consecutive days after operation are shown in figure 6. The temperature was significantly ($P < 0.01$) less in the diclofenac group compared with the control group during the first day after operation.

DISCUSSION

The consumption of morphine was significantly less in the diclofenac group during both days after operation. The patients were not able to co-operate when arriving in the recovery room and therefore we could obtain prestudy pain scores for only two patients in both groups. A 50-cm VAS was used instead of the conventional 10-cm scale, which may be difficult for patients to use immediately after emergence from general anaesthesia when psychomotor skills have not yet recovered [11]. The VAS values in the immediate postoperative period were significantly less in the diclofenac group in which patients received a bolus dose of the study drug during the first 15 min after they had arrived in the recovery room.

After 2 h the VAS values did not differ significantly between the groups, except at 8 h and for both mornings after operation when the diclofenac group had significantly less pain. This difference may be a result of less frequent use of the PCA device during the night, as the patients did not initiate the system while asleep. Also, the VRS for shoulder pain was greater in the control group on the first morning after operation.

Interestingly, the slope of the morphine consumption curve decreased after the first 24 h in the diclofenac group, but not in the placebo group. Thus the mean consumption of morphine in the diclofenac group during the second day after operation was only 14 mg—less than 25 % of the dose required by the control group. NSAID may have reduced the pain on the second day after operation by decreasing inflammation at the wound. Another explanation could be acute tolerance to morphine with larger doses [15]. The fact that 10 patients in the control group required additional i.m. doses of morphine indicates that the programming of the PCA device had been too cautious.

Diclofenac has been shown previously to be effective in pain following orthopaedic surgery [4] and to have varying effects after abdominal surgery [16, 17]. No previous studies exist on its use for post-thoracotomy pain. Jones and colleagues [7] have shown that lysine acetyl salicylate 1.8 g 6-hourly after major thoracic surgery provides pain relief similar to that derived from an infusion of morphine 10 mg 6-hourly. In a recent study by Pavy, Medley and Murphy [8], indomethacin suppositories 200 mg daily given after thoracic surgery reduced the 48-h consumption of papaveretum by 30 %, which was clearly less than the 67 % reduction of morphine consumption in the present study. In Pavy's study, the patients in the indomethacin group had significantly less pain after physiotherapy than the patients in the control group. However, the indomethacin group patients had also significantly less pain at all evaluation times, indicating that the control patients may not have received enough papaveretum, which would explain the smaller opioid sparing effect of indomethacin in their study compared with the results of the present study. Other factors such as the different NSAID and routes of administration used may also have had an effect.

One of the objectives of this study was to find out if any reduction in the consumption of morphine would be reflected in improved blood-gas analyses. The increase in the arterial $P\text{CO}_2$ compared with preoperative values was, indeed, significantly smaller in the dicloflenac group. The same phenomenon has been reported in at least two previous studies in which either i.m. ketorolac or i.m. diclofenac was given for pain relief after abdominal surgery in a similar experimental setting using PCA. The simplest explanation for the difference in the increase in Pa_{CO_2} would be the reduced consumption of morphine in the diclofenac group. However, other causes such as the lower body temperature and metabolic rate should be considered. These factors could also explain the observed beneficial effects of diclofenac infusion on arterial oxygenation. It should be noted that prostaglandin inhibitors have been shown to potentiate hypoxic pulmonary vasoconstriction and to improve peripheral tissue perfusion after coronary artery bypass surgery [18].

In the present study, diclofenac had no effects on haemostasis compared with the control group. A previous study showed that there was no increase in perioperative blood loss during transurethral prostatectomy after oral diclofenac [19]. In another study, it was reported that i.m. diclofenac 75 mg increased the capillary bleeding time, which was however, unaffected, by the same dose when given i.v. [20]. The platelet counts alone do not provide much information about the effects of NSAID on the thrombocyte function and, besides, the platelet count is affected by bleeding and volume correction and should therefore at least be corrected with the PCV. The platelet adhesion test measures the proportional amount of functional thrombocytes and should therefore be a good indicator of any effects of the NSAID on thrombocyte function. Thromboelastography is a qualitative measure of viscoelastic clot strength and it examines whole blood coagulation: interactions of the protein coagulation cascade, fibrinogen and the platelet surface are assessed as a total unit. No difference was found either in the platelet adhesion test or in any thromboelastography parameter between the groups at 2 h from the beginning of the study. Power and colleagues [21] recently reported that after 1 h from an i.m. injection of diclofenac 1.2 mg kg^{-1}, the platelet aggregation was significantly decreased. However, in their study all patients has been given heparin before operation. The discrepancy in the results could also be caused by the use of different tests and the smaller dose of diclofenac (0.4 mg kg^{-1} by 2 h) in our study. A continuous infusion with smaller plasma concentrations might thus be safer than intermittent large boluses resulting in greater concentrations and having more effect on thromboxane production.

Acute renal failure is one of the potentially most important complications associated with the use of NSAID during and after surgery. It is, therefore, somewhat surprising that so little attention has been paid to this problem in all the studies performed with intra- and postoperative use of NSAID. Renal prostaglandins regulate the maintenance of water balance and the excretion of sodium and potassium. They contribute to the maintenance of renal haemodynamics more under adverse conditions than under normal circumstances [22]. Therefore, inhibition of prostaglandin synthesis may have profound consequences for renal blood flow and glomerular filtration rate when it is superimposed on a preceding haemodynamic insult such as hypovolaemia, hypotension [23], salt depletion [24] or heart failure [25]. Anaesthesia and surgery can decrease renal blood flow because of possible hypovolaemia and hypotension. Moreover, the stress response triggered by surgery increases secretion of antidiuretic hormone (ADH), which normally stimulates the production of medullary prostaglandins capable of moderating the tubular effects of ADH by inhibition of the generation of cAMP. NSAID have also been shown to enhance the effects of exogenous vasopressin.

As the majority of the patients in this study underwent either pneumonectomy or lobectomy, the amount of i.v. fluids was restricted to prevent postoperative pulmonary complications. This lower volume of i.v. crystalloids than that recommended generally for surgical patients [26] for the first day after operation, combined with a possible stress response, was manifested as a significantly smaller urine output in the diclofenac group compared with the small urine output in the control group. Fortunately, diuresis was normal during the second day after operation and serum creatinine concentrations did not increase.

A well tailored postoperative pain treatment requires careful consideration of the possible risks and benefits the patient may have from the treatment. If effective but invasive methods such as extradural local anaesthetics and opioids are not feasible, a continuous infusion of diclofenac 2 mg kg^{-1}/24 h during two days after thoracic surgery seems a valuable alternative, as it significantly reduces morphine consumption and improves analgesia and arterial oxygenation and does not interfere with platelet function or bleeding. However, as the diclofenac infusion significantly reduced the urine output during the first day after operation, it should be used cautiously, if at all, in patients who are at high risk of developing renal problems during surgery. Special attention should be paid to the fluid balance and urine output. It might also be safer to start the infusion only after surgery.

ACKNOWLEDGEMENT

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EFFECTS OF KETOROLAC TROMETAMOL ON RENAL FUNCTION

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SUMMARY

We have compared the renal effects of ketorolac trometamol 10 mg administered 4-hourly by intermittent i.m. injection or by continuous i.m. infusion with placebo in a double-blind study in 67 patients who had undergone upper abdominal surgery. Ketorolac was supplemented during the 48-h postoperative study period with bolus doses of morphine delivered by a patient controlled analgesia system. The only significant effect of ketorolac on renal function compared with patients who received placebo was reduced excretion of potassium. The overall changes caused by surgery alone were of much greater magnitude. Bleeding time was increased with ketorolac, but there were no adverse events related to this.

KEY WORDS

Analgesia: postoperative. Analgesics: ketorolac, morphine. Kidney: renal function.

Ketorolac trometamol is a new non-opioid analgesic of the non-steroidal anti-inflammatory (NSAID) class. It has been shown to provide a valuable morphine sparing effect when used to supplement opioid analgesia after upper abdominal surgery [1, 2] and, in some studies, to have analgesic activity comparable to that of morphine [3, 4]. Its principal advantage is lack of depression of the cardiovascular and respiratory systems [5]. A major pharmacological activity of NSAID is reduction of prostaglandin synthesis by inhibition of the enzyme cyclo-oxygenase. In well hydrated individuals with normal renal function, prostaglandins play no apparent role in regulation of renal blood flow or fluid and electrolyte excretion. However, under conditions of reduced renal blood flow, local synthesis of vasodilating prostaglandins has an important role in maintaining renal homeostasis. All NSAID may then cause renal insufficiency by arteriolar vasoconstriction, with subsequent impairment of renal function [6].

As surgery and anaesthesia are associated with activation of renal homeostatic mechanisms, the present study was designed to assess the renal effects of ketorolac administered for 48 h after major surgery.

PATIENTS AND METHODS

We studied 67 patients undergoing elective upper abdominal surgery in a double-blind, placebo-controlled study. The study was approved by the Hospital Ethics Committee and all patients were visited before surgery, the nature of the trial explained, and written informed consent obtained. Exclusion criteria included respiratory insufficiency, hepatic or renal impairment and abuse of alcohol or drugs. A standard anaesthetic was administered to all patients and consisted of premedication with temazepam 20–40 mg, induction with thiopentone 3–6 mg kg^{-1} and maintenance with nitrous oxide, oxygen and enflurane supplemented with alfentanil.

Patients were allocated randomly and in double-blind fashion to one of three groups to receive: continuous i.m. infusion of ketorolac with intermittent injections of placebo (continuous group); intermittent i.m. injections of ketorolac with continuous infusion of placebo (intermittent group); continuous and intermittent administration of placebo (placebo group).

Patients allocated to the continuous ketorolac group received a continuous i.m. infusion of ketorolac. A loading dose was infused at a rate of 12.5 mg h^{-1} for 30 min to achieve a steady state concentration rapidly and the dose was then reduced to 2.5 mg h^{-1} for the duration of the study. They also received intermittent i.m. injections of saline every 4 h. The continuous and intermittent doses were administered into the deltoid muscle through one site via a non-return valve.

Patients in the intermittent ketorolac group received intermittent i.m. injections of ketorolac 10 mg every 4 h and an i.m. infusion of saline at rates to match those in the continuous group.

Patients in the placebo group received intermittent injections and continuous infusions of saline as for the other groups.

At the completion of surgery, each patient was connected to the i.m. delivery system and to a patient controlled analgesia (PCA) apparatus [7] set to

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deliver i.v. bolus doses of morphine 0.02 mg kg^{-1} with a lockout time between doses of 2 min.

Three 24-h collections of urine were made: one on the day before surgery and one on each of the two study days. Blood samples were taken for assessment of renal function at the preoperative visit and at the end of each 24-h urine collection to coincide with the start or end of the appropriate urine collection. The primary variables measured were urine output, creatinine and urea clearance, urine osmolarity, free water clearance and sodium and potassium output. The following formulae were used to calculate the measures of renal function:

Creatinine clearance (ml min^{-1}) =

$$\frac{\text{urine creatinine (mmol litre}^{-1})}{\text{serum creatinine } (\mu\text{mol litre}^{-1})} \times 1000 \times \text{urine volume (ml min}^{-1})$$

Urea clearance (ml min^{-1}) =

$$\frac{\text{urine urea (mmol litre}^{-1})}{\text{serum urea (mmol litre}^{-1})} \times \text{urine volume (ml min}^{-1})$$

Free water clearance (ml min^{-1}) =

$$\frac{(1-\text{urine osmolarity})}{\text{plasma osmolarity}} \times \text{urine volume (ml min}^{-1})$$

Sodium output (μmol litre^{-1}) =

$$\text{urine sodium (mmol litre}^{-1}) \times \text{urine volume (ml min}^{-1})$$

Potassium output (μmol litre^{-1}) =

$$\text{urine potassium (mmol litre}^{-1}) \times \text{urine volume (ml min}^{-1})$$

Bleeding times were measured using a Simplate II device [8] before operation and at 24 h after the start of drug administration.

Patient characteristics were analysed using Student's t test or chi-square test as appropriate. The measures of renal function were analysed using a repeated measures analysis of variance for the difference from baseline data. The factors included were treatment, between-patient error, study day and treatment by day interaction. In the absence of a statistically significant treatment by day interaction, results for the two study days were averaged in the presentation of the results. All three paired comparisons between treatments were carried out by calculating the ratio of the estimated difference between treatments to its standard error (SED) (based on the between patient error) and referring this to the t distribution. A one-way analysis of variance was performed for bleeding times using differences from baseline, and paired comparisons were made.

RESULTS

Sixty-one patients completed the 48 h of the study, and an additional two patients completed 24 h. An additional four patients were withdrawn before 24 h. Withdrawals occurred because of equipment or cannula failure or because of patient request. There were no withdrawals from the study because of adverse events. Patients who received ketorolac were significantly younger than those who received placebo ($P < 0.05$) but there were no differences in sex or weight between the groups (table I).

TABLE I. *Patient data (mean (range or* SD*)). *$P < 0.05$ compared with placebo*

	Continuous ketorolac ($n = 19$)	Intermittent ketorolac ($n = 23$)	Placebo ($n = 21$)
Sex (M:F)	9:10	10:13	10:11
Age (yr)	47.2* (27–71)	48.6* (23–68)	56.1 (42–68)
Weight (kg)	63.5 (9.6)	62.7 (12.1)	68.3 (12.0)

TABLE II. *Urine output (mean* (SD*)). CI = Confidence interval*

	Continuous ketorolac ($n = 15$)	Intermittent ketorolac ($n = 15$)	Placebo ($n = 16$)
Output (ml min^{-1})			
Baseline	0.82 (0.44)	0.98 (0.45)	1.01 (0.65)
Day 1	0.71 (0.46)	0.56 (0.51)	0.71 (0.41)
Day 2	1.46 (0.71)	1.29 (0.59)	1.55 (0.78)
Mean diff. from baseline of 2 days	0.27	−0.05	0.12

	P	Estimated diff.	95% CI
Comparison of effects			
Ketorolac intermittent *vs* continuous	0.19	−0.32	−0.80–0.16
Ketorolac intermittent *vs* placebo	0.47	−0.17	−0.64–0.30
Ketorolac continuous *vs* placebo	0.53	0.15	−0.32–0.63
Difference between days	< 0.01		
Treatment by day interaction	0.92		

The mean urine output for the first 24 h after operation was less than the baseline output, whereas the mean output for the second 24 h was greater (table II). This was true for all treatments and the analysis of the change from baseline showed that the difference between days 1 and 2 was significant ($P < 0.01$). However, the treatment by day interaction was not significantly different ($P = 0.92$), so there was no evidence that the difference between days differed from one treatment group to another. The results for the two days have been pooled and the analysis shows that there was no significant difference between any pair of treatment means.

Creatinine clearances decreased from baseline on day 1, followed by an increase from baseline on day 2 (table III). The difference between days was statistically significant ($P = 0.02$) but, again, there was no evidence that this difference varied across treatment groups ($P = 0.55$). Paired comparison showed no difference between any pair of treatment means.

Urea clearance also decreased from baseline on day 1, followed by an increase from baseline on day 2 (table IV). The difference between days was statistically significant ($P < 0.01$), but there was no evidence of an interaction between treatment and study day ($P = 0.86$). There were no significant differences between any pair of treatment means.

Urine osmolarity changed little from baseline to day 1 for the ketorolac groups, whereas the placebo

TABLE III. *Creatinine clearance (mean (SD)). CI = Confidence interval*

	Continuous ketorolac ($n = 14$)	Intermittent ketorolac ($n = 10$)	Placebo ($n = 15$)
Clearance (ml min^{-1})			
Baseline	86.5 (42.3)	84.4 (58.2)	84.8 (36.5)
Day 1	79.7 (39.7)	60.3 (25.0)	81.5 (43.9)
Day 2	109.2 (60.1)	98.0 (49.7)	91.6 (31.9)
Mean diff. from baseline of 2 days	7.95	−5.26	1.74

	P	Estimated diff.	95% CI
Comparison of effects			
Ketorolac intermittent *vs* continuous	0.49	−13.21	−51.66–25.24
Ketorolac intermittent *vs* placebo	0.71	−7.00	−44.92–30.92
Ketorolac continuous *vs* placebo	0.72	6.21	−28.30–40.72
Difference between days	< 0.02		
Treatment by day interaction	0.55		

TABLE IV. *Urea clearance (mean (SD)). CI = Confidence interval*

	Continuous ketorolac ($n = 13$)	Intermittent ketorolac ($n = 11$)	Placebo ($n = 13$)
Clearance (ml min^{-1})			
Baseline	36.7 (18.6)	35.7 (18.9)	41.0 (18.8)
Day 1	32.2 (25.7)	23.8 (14.7)	32.7 (23.9)
Day 2	51.4 (23.8)	45.9 (25.1)	48.8 (17.3)
Mean diff. from baseline of 2 days	5.07	−0.88	−0.20

	P	Estimated diff.	95% CI
Comparison of effects			
Ketorolac intermittent *vs* continuous	0.48	−5.95	−22.94–11.04
Ketorolac intermittent *vs* placebo	0.94	−0.68	−17.67–16.31
Ketorolac continuous *vs* placebo	0.52	5.27	−11.00–21.54
Difference between days	< 0.01		
Treatment by day interaction	0.86		

TABLE V. *Urine osmolarity (mean (SD)). CI = Confidence interval*

	Continuous ketorolac ($n = 11$)	Intermittent ketorolac ($n = 11$)	Placebo ($n = 13$)
Osmolarity (units)			
Baseline	572.5 (165.8)	614.8 (309.6)	570.8 (167.4)
Day 1	550.1 (317.1)	643.8 (229.8)	725.0 (259.1)
Day 2	329.7 (173.3)	316.2 (84.3)	325.3 (192.1)
Mean diff. from baseline of 2 days	−132.6	−134.8	−45.6

	P	Estimated diff.	95% CI
Comparison of effects			
Ketorolac intermittent *vs* continuous	0.99	−2.2	−238.3–233.9
Ketorolac intermittent *vs* placebo	0.43	−89.2	−316.0–137.6
Ketorolac continuous *vs* placebo	0.44	−87.0	−313.8–139.8
Difference between days	< 0.01		
Treatment by day interaction	0.38		

TABLE VI. *Sodium output (mean (SD)). CI = Confidence interval*

	Continuous ketorolac ($n = 14$)	Intermittent ketorolac ($n = 11$)	Placebo ($n = 15$)
Output (μmol min^{-1})			
Baseline	89.5 (66.3)	95.6 (59.7)	110.9 (70.0)
Day 1	25.2 (22.0)	29.2 (27.8)	46.1 (35.2)
Day 2	56.5 (42.5)	42.3 (34.3)	82.1 (50.9)
Mean diff. from baseline of 2 days	−48.7	−59.8	−46.7

	P	Estimated diff.	95% CI
Comparison of effects			
Ketorolac intermittent *vs* continuous	0.68	−11.2	−66.1–43.7
Ketorolac intermittent *vs* placebo	0.63	−13.1	−67.2–41.0
Ketorolac continuous *vs* placebo	0.94	−1.9	−52.5–48.7
Difference between days	< 0.01		
Treatment by day interaction	0.41		

group had a marked increase (table V). In all three groups, values decreased to about 50% of their baseline values on day 2. The difference between days was significant ($P < 0.01$), but the treatment by day interaction did not approach significance ($P = 0.38$).

Sodium output decreased from baseline to day 1 followed by an increase on day 2 (table VI). The difference between days was significant ($P < 0.01$), but there was no difference between treatments ($P = 0.41$).

Potassium output decreased from baseline to day 1 for both ketorolac groups, but increased for placebo (table VII). There was little change from day 1 to day 2. The difference between days did not approach significance ($P = 0.50$), but there was a significant difference between placebo and intermittent ($P = 0.02$) and continuous ketorolac ($P = 0.04$). There was no evidence of a difference between the two ketorolac groups ($P = 0.58$).

There were no significant differences between the groups in arterial pressure, heart rate, haematological or biochemical analyses, including plasma potassium

TABLE VII. *Potassium output (mean (SD)). CI = Confidence interval*

	Continuous ketorolac ($n = 14$)	Intermittent ketorolac ($n = 11$)	Placebo ($n = 15$)
Output (μmol min^{-1})			
Baseline	30.5 (17.7)	33.3 (27.8)	35.3 (14.2)
Day 1	25.4 (15.5)	23.1 (7.6)	47.9 (31.7)
Day 2	29.1 (14.5)	26.5 (18.0)	52.3 (52.5)
Mean diff. from baseline of 2 days	−3.3	−8.5	14.8

	P	Estimated diff.	95% CI
Comparison of effects			
Ketorolac intermittent *vs* continuous	0.58	−5.2	−24.1 to 13.7
Ketorolac intermittent *vs* placebo	0.02	−23.3	−42.0 to −4.7
Ketorolac continuous *vs* placebo	0.04	−18.1	−35.6 to −0.6
Difference between days	0.59		
Treatment by day interaction	1.0		

TABLE VIII. *Analysis of bleeding times (s). CI = Confidence interval*

	Continuous ketorolac	Intermittent ketorolac	Placebo
Times (s)			
Baseline	248.1 ($n = 22$)	206.3 ($n = 24$)	232.5 ($n = 21$)
Day 1	304.8 ($n = 20$)	237.7 ($n = 23$)	220.1 ($n = 21$)
Mean diff. from baseline	54.7 ($n = 20$)	35.2 ($n = 23$)	−12.2 ($n = 21$)
95% CI	19.9–89.6	2.7–67.7	−46.2–21.8

	P	Estimated diff.	95% CI
Comparison of effects			
Ketorolac intermittent *vs* continuous	0.42	−19.5	−67.1–28.1
Ketorolac intermittent *vs* placebo	0.05	47.4	0.4–94.4
Ketorolac continuous *vs* placebo	0.01	66.9	18.2–115.6

concentration. Bleeding times increased from baseline in patients who received ketorolac compared with placebo, but there was no significant difference between intermittent and continuous methods of administration (table VIII).

The most common side effects were nausea or vomiting and urinary retention, but there were no differences between groups.

DISCUSSION

Ketorolac has the principal advantage over opioid analgesics of lack of cardiorespiratory effects following administration [5]. Ketorolac may therefore provide useful analgesia, either alone or as a supplement to an opioid, with minimal depressant effects. The analgesic effects of the ketorolac doses used in this study have been reported previously [2] and demonstrated the expected reduction in prostaglandin production by a significant decrease in postoperative morphine requirements.

All NSAID may affect renal function adversely [9, 10], but this appears to be important mainly in patients who have compromised renal blood flow, which is dependent on renal prostaglandins to maintain adequate glomerular perfusion. In several clinical conditions such as congestive cardiac failure, cirrhosis, hypovolaemia and renal insufficiency, the local production of prostaglandins is essential to maintain renal perfusion. Such patients are therefore at increased risk of renal ischaemia after administration of NSAID.

The main aim of this study was to determine the effect of ketorolac on renal function in the immediate postoperative period. The results of the analysis of renal function indicated that there were changes in renal function in all groups, but no significant differences between any of the groups for any of the measures of renal function except for potassium output, which decreased in patients who received ketorolac. Potassium loss is a well recognized response in the postsurgical period and ketorolac appears to prevent this. This effect would seem to be of little practical significance.

A further objective of the study was to identify if any drug effects were different between the first and second days after operation. For all measures of renal function except potassium output, the analyses showed significant differences between the first and second days. However, the treatment by day interactions were not significant, indicating that the differences between the two days were similar for all treatment groups.

The study incorporated a comparison of intermittent and continuous administration of ketorolac. There were no statistically significant differences between the effects of the two dosing techniques on renal function. However, there was a larger increase in urea and creatinine clearances over the study period in the group who received ketorolac continuously, compared with the intermittent group. This may indicate a tendency to faster improvement in renal function after operation when a small steady state plasma concentration was maintained in comparison with the peaks and troughs of an intermittent regimen.

Ketorolac is known to increase bleeding time [11, 12] because of inhibition of platelet aggregation. The mean increase in bleeding time was 35 s in the intermittent group and 55 s in the continuous group, compared with a decrease of 12 s in the placebo group. The greatest increase observed was 250 s in one patient who received continuous ketorolac, but this was still not greater than the normal range for bleeding time.This is similar to the largest increase reported by Power and colleagues [12] of 214 s in one patient.

In conclusion, the analyses of renal function showed consistently that there was a marked difference between the two postoperative study days and it appears that changes in renal function caused by surgery and the subsequent recovery period were of more clinical importance than any drug induced effect.

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PHARMACOKINETICS OF PROPOFOL DURING AND AFTER LONG TERM CONTINUOUS INFUSION FOR MAINTENANCE OF SEDATION IN ICU PATIENTS†

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SUMMARY

The pharmacokinetics of propofol administered as long term infusions were determined in 12 intensive care unit patients (two female; mean age 58 yr, mean weight 66.9 kg) requiring sedation during mechanical ventilation. Patients were recruited after having been administered propofol for 24 h. Blood samples for analysis of propofol were taken during the infusion (mean duration 85.6 h; mean rate 2.58 mg kg^{-1} h^{-1}) and for up to about 42 h after its termination. The median propofol total body clearance, derived from the apparent steady state propofol blood concentrations during infusion, was 2.11 litre min^{-1}. One patient died during the infusion, from multi-organ failure secondary to a pre-existing septicaemia, and in one other patient no sampling was possible during the first 30 min after infusion; full elimination data were obtained for 10 patients. After termination of the infusion, propofol blood concentrations declined rapidly, with an overall mean decrease of 50% over the first 10 min; thereafter the decline was more gradual. The elimination profile was triphasic in seven patients and biphasic in three patients. Mean half-lives for the three phases were 1.81 (n = 10) min, 70.9 (n = 7) min and 1411 (n = 11) min. There was no apparent trend in the terminal phase half-life with the duration of sampling after infusion.

KEY WORDS

Anaesthetics, intravenous: propofol. Pharmacokinetics: propofol. Intensive care.

Propofol (2,6-diisopropylphenol) is approved for maintenance of anaesthesia by a technique of administration of small bolus doses, or by continuous infusion. Recovery from anaesthesia is rapid and psychometric assessment indicates that patients performance and co-ordination return quickly [1], and there is a small incidence of post-anaesthesia nausea and vomiting [2].

Many intensive care unit (ICU) patients require sedation for prolonged periods. The aim of this level of sedation is to keep the patient comfortable in spite of the level of surrounding activity and to prevent resistance to mechanical ventilation. There has been an increased interest in the use of propofol since the withdrawal of alphaxalone–alphadolone (Althesin) because of the risk of anaphylactoid reactions [3] and the high incidence of impaired steroidogenesis with etomidate [4].

The pharmacokinetics of propofol have been studied after single bolus doses to paediatric patients [5], young adults [6,7], elderly subjects [8] and in subjects with hepatic impairment [9] and those with renal dysfunction [10]. Gepts and colleagues [11] studied the pharmacokinetics during and following zero order infusions of propofol and Cockshott and colleagues [12] have reported data for a bolus and infusion regimen. However, only limited pharmacokinetic data have been reported for prolonged sedative infusions. Beller and colleagues [13] studied the decline of propofol concentrations for 90-min periods after infusions lasting 1, 2, 3 and 4 days, whilst Albanese and co-workers [14] have reported clearance, steady state, volume of distribution and terminal elimination half-life data for patients sedated with propofol for 3 days.

In this study we have measured the apparent steady state propofol concentrations during sedative infusions and the decline in propofol concentration for about 42 h after the termination of the infusion.

PATIENTS AND METHODS

The study was approved by the hospital's Ethics Committee. As all patients were unable to respond, prospective informed consent was obtained from each patient's next of kin. Male or female patients admitted to the ICU were eligible for the study if aged more than 16 yr and expected to require a period of elective mechanical ventilation and sedation lasting for at least 48 h.

Patients were excluded from the study if they had known allergy to propofol, were pregnant, had a head injury or severe disorders of lipid metabolism, were undergoing haemodialysis, peritoneal dialysis or haemofiltration, had severe hepatic disease or

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TABLE I. *Patient data*

Patient No.	Sex	Age (yr)	Weight (kg)	Apache II Grade	Diagnosis
1	M	27	38.6	9	Laparotomy for ruptured spleen and intra-abdominal sepsis.
2	M	56	71.8	6	Laparotomy for drainage of multiple intra-abdominal abscesses and exteriorization of small bowel fistulae.
3	M	53	87.8	14	Cardiovascular collapse 18 h after laparotomy for closure of multiple bowel fistulae and splenectomy.
4	M	67	53.2	15	Acute respiratory failure 4 days after gastrectomy. Chronic obstructive airways disease.
5	F	60	42.0	17	Acute respiratory failure. Right lower lobe pneumonia. Chronic obstructive airways disease.
6	M	64	52.4	17	Post-op. emergency laparotomy: perforated duodenal ulcer, resection of colon; septicaemic shock.
7	M	64	72.6	7	Acute respiratory failure. Right lower lobe pneumonia. Conjestive heart failure.
8	M	46	85.4	5	Fall from 12 m. Lung contusion. Left haemopneumothorax. Splenic rupture, post-op. laparotomy.
9	M	68	69.0	27	Sigmoid colectomy for severe diverticular disease. Septicaemia. Subacute bacterial endocarditis with mitral and aortic incompetence.
10	F	66	69.5	35	Post-op. Charnley–Hastings hemiarthropathy. Respiratory failure. Atrial fibrillation.
11	M	65	70.6	22	Respiratory failure 6 days after emergency abdominal aortic aneurysm repair. Bronchopneumonia. Chronic obstructive airways disease. Bronchiectasis.
12	M	55	90.1	28	Laparotomy for ruptured spleen and intra-abdominal sepsis.
Mean		58	66.9	17	
SD		12	17.1	10	

TABLE II. *Duration and rate of administration (mean, including bolus doses (range, excluding bolus doses)) of the infusion of propofol. † Excludes anaesthetic infusion*

Patient No.	Infusion duration (h)	Rate of admin. ($mg\ kg^{-1}\ h^{-1}$)
1	70.8	5.41 (3.11–8.28)
2	67.9	0.99 (0.97)
3	65.3	0.79 (0.68–1.14)
4	86.2	2.16 (1.88–2.26)†
5	57.9	2.51 (1.19–2.86)
6	61.3	1.17 (1.15–1.91)
7	86.8	2.39 (0.69–5.51)
8	90.5	2.10 (0.94–2.93)
9	178.8	2.28 (1.45–2.90)
10	92.6	2.00 (1.15–2.16)
11	32.4	6.40 (3.54–8.50)
12	137.2	2.79 (2.22–3.33)
Mean	85.6	2.58
SD	38.8	1.69

were grossly obese (> 20 % greater than ideal body weight). All patients had daily monitoring of serum concentrations of urea, creatinine and electrolytes, liver function tests, RBC and clotting screen.

Propofol was administered as a 1 % oil in water emulsion; the infusion was given via a central vein and was adjusted to achieve sedation at the desired level together with opioids as required. The pharmacokinetic assessment began only after the patient had received a continuous infusion for 24 h and when a stable infusion rate had been achieved.

Arterial blood was obtained from a cannula inserted in the radial artery. The cannula was kept patent with low-dose (1.0 iu ml^{-1}) heparin. The deadspace volume was removed before each sampling. Blood samples (2 ml) were collected in tubes containing potassium oxalate and were cooled to 4 °C within 30 min. Samples were stored at 4 °C until required for analysis by the HPLC–fluorescence method described by Plummer [15]. Quality control of the assay was achieved by repeat analysis of 50 % of all samples in separate assays; further replication was performed when duplicates differed by more than approximately 10 %.

Blood samples were taken at the start of the assessment and, where possible, every 6–12 h thereafter. On discontinuation of the infusion, blood samples were taken at 0, 2, 4, 6, 8, 10, 20, 30, 45, 60, 90, 120, 180, 240, 300, 360, 420, 480, 540, 600 and 720 min and then, where possible, every 3 h up to 48 h. The sample volume was increased to 5 ml from 30 min after the end of the infusion to ensure adequate sensitivity of the propofol assay.

Pharmacokinetic calculations

In patients in whom the propofol infusion rate had remained constant for at least 5 h, the apparent steady state blood concentration (C_1^{ss}) was used to estimate propofol total body clearance (Cl) as follows:

$$Cl\ (\text{litre min}^{-1}) = \frac{\text{infusion rate (mg min}^{-1})}{C_1^{ss}\ (\text{mg litre}^{-1})}$$

The decline in blood concentrations of propofol after termination of the infusion was fitted by a tri-exponential function of the following form using the extended least squares curve fitting program ELSFIT [16] with a weighting of $1/C$:

$$C_1 = Ae^{-\alpha t} + Be^{-\beta t} + Ce^{-\gamma t}$$

Where C_1 = concentration in blood at any time t after the end of the infusion; A, B and C = intercepts; α, β and γ = slopes of the three exponential phases. Initital estimates for these parameters were derived using the standard feathering tech-

TABLE III. *Apparent steady state blood concentrations* (C_1^{ss}) *and derived clearance* (Cl) *values.* **Data obtained* < 5 *h from an infusion rate change have been excluded*

Patient No.	Infusion: Rate (mg kg⁻¹ h⁻¹)	Infusion: Time at rate* (h)	C_1^{ss} (μg ml⁻¹)	*Cl* (litre min⁻¹)	*Cl* (ml kg⁻¹min⁻¹)
1	4.15	14.5	1.71	1.56	40.4
	4.15	20.5	1.60	1.67	43.2
	4.66	9.5	1.49	2.01	52.1
	8.28	7.8	2.81	1.90	49.1
	8.28	13.4	2.57	2.07	53.7
2	0.97	29.0	0.20	5.80	80.8
	0.97	34.9	0.45	2.58	35.9
	0.97	40.5	0.26	4.46	62.2
	0.97	47.2	0.17	6.83	95.1
	0.97	67.9	0.50	2.32	32.3
3	0.68	13.5	0.45	2.21	25.2
	0.68	31.5	0.52	1.91	21.8
4	2.26	32.8	0.05	40.1	753
	1.88	12.6	1.56	1.07	20.1
5	2.86	42.9	0.97	2.06	49.1
6	1.15	24.1	0.15	6.70	128
	1.15	36.3	0.14	7.17	137
	1.15	41.9	0.12	8.37	160
	1.15	50.0	0.04	25.1	479
	1.15	60.1	0.47	2.14	40.8
	1.15	60.7	0.54	1.86	35.5
7	5.51	5.8	3.16	2.11	29.1
	5.51	11.8	3.25	2.05	28.3
	2.75	11.2	1.54	2.16	29.8
8	1.41	6.0	0.38	5.28	61.8
	1.41	12.0	0.43	4.67	54.7
	1.76	10.0	1.08	2.32	27.2
	2.11	12.0	1.40	2.15	25.1
	2.93	16.8	1.63	2.56	30.0
	2.93	19.5	1.46	2.86	33.4
9	2.17	8.5	1.13	2.21	32.0
	2.17	11.9	1.19	2.10	30.4
	2.17	18.6	1.26	1.98	28.7
	2.17	22.4	1.62	1.54	22.3
	2.17	32.8	1.49	1.67	24.3
	2.17	44.9	1.47	1.70	24.6
	2.90	8.7	1.81	1.84	26.7
	2.90	32.9	1.70	1.96	28.4
	2.90	44.6	1.90	1.75	25.4
	2.46	21.9	1.37	2.07	29.9
	2.46	27.6	1.47	1.92	27.9
	2.46	46.1	1.96	1.44	20.9
10	2.01	18.2	1.56	1.49	21.5
	2.01	40.0	1.54	1.51	21.8
	2.16	15.4	1.71	1.46	21.1
	2.16	33.0	1.64	1.53	22.0
11	7.08	16.3	3.41	2.44	34.6
12	2.77	6.6	2.07	2.01	22.3
	2.77	14.6	1.21	3.44	38.2
	2.77	17.2	1.15	3.62	40.1
	2.77	24.6	1.18	3.53	39.1
	2.77	36.6	1.27	3.28	36.4
	2.77	60.6	1.44	2.89	32.1
	2.77	131.7	1.22	3.41	37.8

nique. The fitting procedure was then repeated using a bi-exponential function. The choice between the two models was based on the Schwarz criterion [17], the residuals of the observed concentrations from the line of best fit and the confidence with which the parameters were defined.

RESULTS

Twelve patients were recruited into the study. One patient (No. 9) died during the period of infusion, from multi-organ failure secondary to a pre-existing septicaemia; there are, therefore, only 11 sets of data for the elimination phase. For one patient (No. 7) it was not possible to obtain blood samples for the first 30 min after termination of the infusion.

Individual and mean demographic and diagnostic data are listed in table I. The mean (SD) duration of administration of propofol was 85.6 (38.8) h; in only one patient was the infusion duration less than 48 h. The mean rate of administration was 2.58 (1.69) mg kg⁻¹ h⁻¹ (table II). Morphine was administered to eight patients in the first 24 h of study, with a mean (SD) dose of 23.4 (24.4) mg (range 2.5–70 mg).

TABLE IV. *Overall and patient median (interquartile range) total body clearance values. Infusion rates are those pertaining at the times when estimates of clearance were made. NC = Not calculated, as difference between two estimates was large*

Patient No.	Infusion rate ($mg\ kg^{-1}\ h^{-1}$)	Total body clearance ($litre\ min^{-1}$)	Total body clearance ($ml\ min^{-1}\ kg^{-1}$)	*n*
1	4.15–8.28	1.90 (0.34)	49.1 (8.9)	5
2	0.97	4.46 (3.22)	62.2 (44.9)	5
3	0.68	2.06	23.5	2
4	1.88	NC	NC	2
5	2.86	2.06	49.1	1
6	1.15	6.94 (6.23)	132.5 (119.2)	5
7	2.75–5.51	2.11 (0.11)	29.1 (1.5)	3
8	1.41–2.93	2.71 (2.35)	31.7 (27.5)	6
9	2.17–2.90	1.88 (0.34)	27.3 (4.9)	12
10	2.01–2.16	1.50 (0.05)	21.7 (0.6)	4
11	7.08	2.44	34.6	1
12	2.77	3.41 (0.64)	37.8 (7.0)	7
Overall		2.11 (1.51)	34.6 (21.8)	

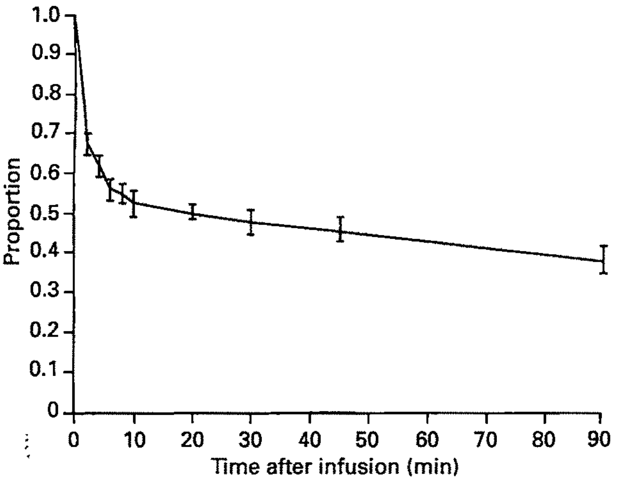

FIG. 1. Mean (SE) proportional decline in blood concentrations of propofol relative to concentration at the end of infusion.

Morphine was administered to seven patients in the second 24 h of study in a dose of 18.2 (16.1) mg (2.5–40 mg). During the sedative infusion administered to patient No. 4, a short period (45 min) of general anaesthesia was required; the infusion rate was increased to 11.3 $mg\ kg^{-1}\ h^{-1}$ for 10 min and then 5.6 $mg\ kg^{-1}\ h^{-1}$ for 35 min; the first pharmacokinetic sample was taken 32.8 h after the end of this period of general anaesthesia.

Apparent steady state blood concentrations and derived *Cl* values for samples from all individuals are summarized in table III. Extremely high estimates of *Cl* were obtained on one sampling occasion for both patients Nos 4 and 6. For patients Nos 2, 6 and 8, several spuriously large *Cl* values were observed; these did not appear to be a consequence of previous changes in infusion rate. In view of the wide intra-patient variability in *Cl*, the median is considered to be the most representative value for this parameter in the patient population from this study. Individual patient median *Cl* values were large (1.5 $litre\ min^{-1}$ or greater), with an overall median *Cl* of 2.11 $litre\ min^{-1}$ (34.6 $ml\ min^{-1}\ kg^{-1}$) (table IV).

After termination of the infusion, propofol concentrations declined rapidly, with an overall mean decrease of about 50% over the first 10 min (fig. 1); thereafter, the decline was more gradual. Propofol blood concentration profiles for all individuals after the termination of the infusion are given in figure 2. The decreases in concentration for seven patients were best fitted by a tri-exponential function (table V); for three patients, data were best fitted by a bi-exponential function and for one patient (No. 7) the lack of any samples during the first 30 min after the termination of the infusion prevented the definition of the early phase(s). There was no apparent trend ($r = 0.18$) in the terminal phase half-life estimates with increase in the period of assessment (fig. 3).

DISCUSSION

Inspection of the *Cl* data did not reveal any consistent temporal trend in *Cl* estimates for any patient; this suggests that blood concentrations were close to their steady state values within the 5-h period, which was set as the mimimum time at any

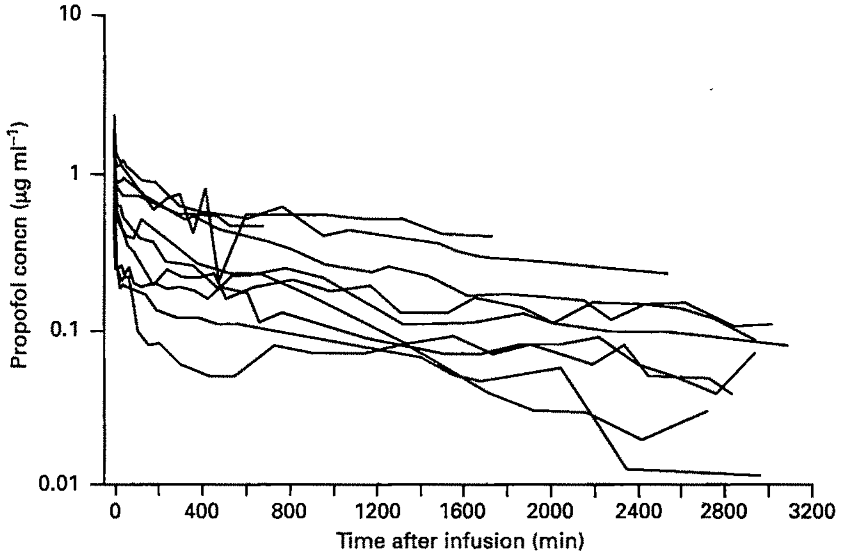

FIG. 2. Individual blood concentrations of propofol after termination of the infusion.

TABLE V. *Post-infusion elimination data. * Defined with low confidence. † Bi-exponential preferred. § Sampling commenced 30 min after infusion; mono-exponential preferred*

Patient No.	Sampling duration (min)	A (μg ml^{-1})	$T_{\frac{1}{2}}^{\alpha}$ (min)	B (μg ml^{-1})	$T_{\frac{1}{2}}^{\beta}$ (min)	C (μg ml^{-1})	$T_{\frac{1}{2}}^{\gamma}$ (min)
1	2538	0.893	1.48	0.643	85.1	0.735	1414
2	2724	0.213	0.69*	0.207	51.0	0.078	2075
3	2941	0.295	3.55	†	†	0.222	1242
4	1730	0.711	2.06	†	†	0.808	1490
5	2835	0.462	2.71	†	†	0.457	729
6	2958	0.270	0.95	0.106	36.7	0.162	975
7	2190	§	§	§	§	0.436	831
8	3090	0.662	0.57	0.503	54.6	0.295	1409
10	677	0.750	1.48	0.188	81.9	0.691	1173
11	3020	0.648	3.54	0.744	145	0.460	1392
12	2931	0.602	1.06	0.391	41.7	0.228	2794
Mean	2512		1.81		70.9		1411
SD	734		1.12		37.6		586

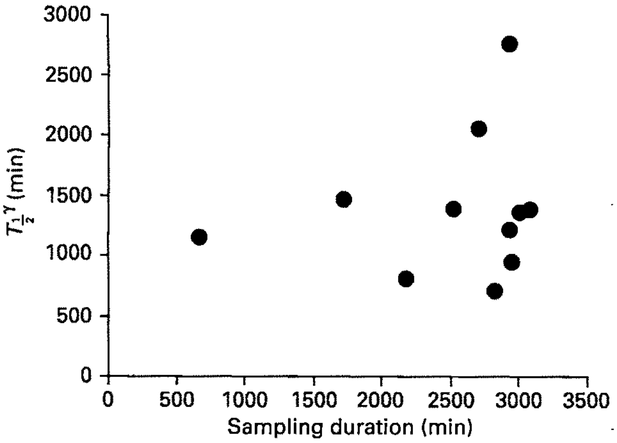

FIG. 3. Relationship between terminal elimination half-life ($T_{\frac{1}{2}}^{\gamma}$) and post-infusion sampling duration.

infusion rate for calculation of *Cl*. The median *Cl* estimate for this patient population (2.11 litre min^{-1}) is similar to data reported for much shorter infusions (about 2 h) at approximately the same rate (1.93 litre min^{-1}) [11,12]. The similarity of the data indicates that the propofol clearance mechanisms in these severely ill intensive care unit patients were not impaired compared with those in the ASA I and II patients in the surgical anaesthesia studies. The clearance of propofol is known to be metabolic [18] and *Cl* is not altered significantly in patients with cirrhosis who received a single bolus dose of propofol [9] or those administered an infusion [19]. These observations are consistent with propofol *Cl* being hepatic blood flow rather than hepatic capacity limited. Patients with severe hepatic impairment were excluded from this present study and the patients studied by Servin and colleagues [9,19] could be considered to have only moderate hepatic dysfunction. Further studies are necessary, therefore, to assess whether or not patients admitted to an intensive care unit with severe hepatic impairment would, on pharmacokinetic grounds, have the same or a reduced propofol sedative dose requirement compared with those with only moderate or no hepatic dysfunction.

The spuriously large *Cl* estimates for several samples from patients Nos 2, 6 and 8 are considerably in excess of the total blood supply to the liver and approximate total cardiac output; although extrahepatic mechanisms for the clearance of propofol have been suggested [7,9,11], *Cl* values of this magnitude have not been reported previously. It seems unlikely that they reflect the true clearance of propofol, but no reason can be given for their occurrence.

Propofol blood concentrations declined by about 50% during the first 10 min after discontinuation of the infusion. For short anaesthetic procedures, the post-infusion decline comprises both distributional and elimination components. During these long sedative infusions, steady state is achieved, with the elimination from blood balanced exactly by input from the infusion. When the infusion is discontinued, this equilibrium is disturbed and propofol concentrations decline much more rapidly than would be expected from the terminal elimination half-life. This is the result of the gradual establishment of a new equilibrium between propofol in blood and that in peripheral compartments. After this new equilibrium has been established, propofol concentrations decline with the half-life of the terminal phase. A similar rapid decline in concentration in the first 90 min after infusion was reported by Beller and colleagues [13] when the recovery profile was assessed at daily intervals after infusions of 3 mg kg^{-1} h^{-1} lasting 24–96 h to patients requiring sedative infusions for trauma. In these patients there was no apparent trend in the rate of decline in propofol concentration over the 4 days of assessment.

The mean half-life value for the second phase ($T_{\frac{1}{2}}^{\beta}$, 70.9 min) was about double those reported for infusions of short duration (about 30 min) [11,12,19 (controls)] with sampling for 8 h after infusion. Where longer (24-h post-dose) sampling times have been used after single bolus doses of propofol [8,20], second phase half-lives for young adults were about 50 min. The third phase half-life in this present study ($T_{\frac{1}{2}}^{\gamma}$, 1411 min) was appreciably longer than values reported for infusions of short duration (200–500 min), but is in good agreement with that reported by Albanese and colleagues [14] (1878 (SD) 672 min) when sampling for 48 h after an infusion at 3 mg kg^{-1} h^{-1} for 3 days to patients sedated for mechanical ventilation. Kirkpatrick and co-workers [8] suggested that the longer terminal phase half-life observed in their study in young adults (674 min) compared with those from earlier studies (184–382 min) may be related to their longer sampling period of 24 h compared with 8–12 h. However, over the range of post-infusion sampling periods in this present study (677–3090 min) there was no apparent trend in terminal phase half-life values. In normal clinical use, even for long periods of sedation, the terminal elimination phase is unlikely to be significant in determining the return of responsiveness. However, if a patient were deeply anaesthetized for the periods used in this study, the terminal phase would be expected to play a major role in the recovery profile.

From the bolus dose micro-rate constant data reported by Kirkpatrick and colleagues [8] for young patients, the terminal phase is estimated to account for about 40 % of the total area under the curve. On this basis, for a terminal phase having a half-life of 1411 min it would be predicted that 66 % of steady state would be achieved by 5 h, 70 % at 10 h, 78 % at 20 h and 88 % at 40 h. The lack of any consistent trend in *Cl* values over the long periods of assessment in this present study indicates that the effective half-life of the terminal phase in defining the approach to steady state is much shorter. This suggests that the terminal phase may only be of any consequence at very low propofol concentrations representing, under these circumstances, the slow return of propofol from a poorly perfused tissue compartment.

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USE OF MIVACURIUM CHLORIDE BY CONSTANT INFUSION IN THE ANEPHRIC PATIENT

B. J. PHILLIPS AND J. M. HUNTER

SUMMARY

Twenty anephric and 20 healthy patients received a bolus dose of mivacurium 150 μg kg^{-1}. When the first EMG response (T1) of the train-of-four had recovered to 5% of control (T0), an infusion of mivacurium 10 μg kg^{-1} min^{-1} was started and adjusted to keep T1 at 5%. Ten patients in each group were given neostigmine 35 μg kg^{-1} when the infusion was stopped when T1/T0 had recovered to 20%; in the others recovery was spontaneous. After the bolus dose of mivacurium, mean (SD) depression of T1 was greater in the anephric group than in the normal group (98.4 (3.5) vs 96.8 (4.4)%; $P < 0.01$) and recovery of T1/T0 to 5% was slower (15.3 (6.9) vs 9.8 (3.5) min; $P < 0.01$). Anephric patients required a slower infusion rate (6.3 (1.9) vs 10.4 (2.8) μg kg^{-1} min^{-1}; $P < 0.001$). Neostigmine hastened recovery of both T1/T0 and T4/T1 in both groups. Spontaneous recovery of T1/T0 (from 25% to 75%) after the infusion was also slower in anephric patients (12.2 (8.2) vs 7.7 (1.2) min; $P < 0.05$). Plasma cholinesterase activity was less in the anephric group (785 (207) vs 943 (217) iu litre^{-1}; $P < 0.05$) and there was a (negative) correlation overall between cholinesterase activity and time to 5% recovery of T1/T0 after the bolus dose ($r = -0.42$; $P < 0.02$). We conclude that patients with chronic renal failure may require a reduced dose of mivacurium.

KEY WORDS

Complications: renal failure. Enzymes: cholinesterase. Neuromuscular relaxants: mivacurium infusion.

The new short-acting non-depolarizing neuromuscular blocking agent mivacurium is thought to be metabolized in plasma by pseudocholinesterase, at about 88% of the rate of metabolism of suxamethonium [1]. It is possible that a small amount may also be excreted unchanged in urine [2]. Patients with end-stage renal failure may have reduced plasma cholinesterase activity. The cause of this is uncertain, but it is thought not to be caused by the techniques of haemo- or peritoneal dialysis [3, 4]. It was decided to perform a pharmacodynamic study of mivacurium in patients with end-stage renal failure compared with healthy controls. As this drug has a short elimination half-life of about 17 min [5], we used a bolus dose followed by a constant infusion of the drug.

PATIENTS AND METHODS

This study was approved by the Committee on Safety of Medicines and our Hospital Ethics Committee. All patients gave informed written consent. We studied 20 patients in chronic renal failure (group 1; ASA II or III) and 20 healthy patients (group 2; ASA I or II) undergoing elective surgery requiring neuromuscular block, in order of presentation. The renal failure patients were undergoing vascular access surgery, insertion of peritoneal dialysis catheter or graft nephrectomy; patients undergoing renal transplantation were not included, because of possible elimination of mivacurium by the kidneys during the procedure. Patients in group 2 were undergoing general or gynaecological procedures. Patients were excluded if they had a clinical history of neuromuscular disorder, asthma, chronic alcoholism, difficult tracheal intubation or were receiving drugs known to interfere with neuromuscular transmission, such as quinine, aminoglycoside antibiotics or antidepressants. All the patients had plasma urea and electrolyte concentrations, liver function tests, haemoglobin concentrations, cholinesterase activity, dibucaine and fluoride number estimated before operation, but the results of the last three were not known until after surgery. ASA II or III patients had a preoperative chest x-ray and electrocardiograph.

The patients were premedicated with diazepam 5–10 mg orally, 2 h before operation. Anaesthesia was induced with midazolam 50 μg kg^{-1}, fentanyl 1–2 μg kg^{-1} and thiopentone 3–5 mg kg^{-1} and maintained with 70% nitrous oxide in oxygen whilst electromyographic monitoring was commenced on one arm and two i.v. infusions inserted in the other.

The ulnar nerve was stimulated at the wrist every 12 s using the train-of-four (TOF) technique and the compound muscle action potential of adductor pollicis recorded, as described previously, using the Medelec MS6 [6]. Electromyographic monitoring

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was continued throughout anaesthesia. The hand was covered in gauze padding and hand temperature was monitored continuously in cases lasting more than 1 h, using a Portex PSB "Bi Temp" temperature monitor. The temperature remained greater than 32 °C in all cases.

After control readings of the TOF had been recorded for at least 2 min, a bolus dose of mivacurium 150 $\mu g\,kg^{-1}$ was given into a dedicated infusion in the opposite arm. Tracheal intubation was then attempted at 2 min and graded as excellent (no movement, vocal cords abducted), good (cords abducted, some diaphragmatic movement), poor (intubation achieved, but cord and diaphragmatic movement present) or impossible [7]. If intubation failed at 2 min, it was attempted 1 min later. Any evidence of histamine release at the site of injection of mivacurium or proximally was noted. Heart rate and arterial pressure were recorded immediately before injection of the bolus dose and at 1-min intervals for 5 min thereafter, using a Cardiocap automatic pressure recorder (Datex). At the end of this period, arterial pressure was recorded at 5-min intervals using the same equipment. Bolus doses of fentanyl 0.5–1.0 $\mu g\,kg^{-1}$ and midazolam 25 $\mu g\,kg^{-1}$ were given as indicated by any increase in heart rate or arterial pressure. No volatile agent was used throughout the procedure.

When the first twitch of the TOF (T1) had returned to 5 % of control (T0), a constant infusion of mivacurium 10 $\mu g\,kg^{-1}\,min^{-1}$ in 5 % glucose was started through the same dedicated i.v. infusion, using a constant infusion pump (AVI 270: 3M Health Care Group). T1/T0 was measured every 3 min and the infusion rate adjusted immediately by increments or decrements of 1 $\mu g\,kg^{-1}\,min^{-1}$ to maintain T1/T0 at 5 ± 2 %. If this value did not decrease to less than 5 % after the bolus dose, the infusion was commenced when T1/T0 started to increase.

The mivacurium infusion was stopped towards the end of surgery and, when T1/T0 had recovered to 20 %, the first 10 patients in each group (groups 1a and 2a) were given neostigmine 35 $\mu g\,kg^{-1}$, accompanied by atropine 15 $\mu g\,kg^{-1}$. In the second 10 patients in each group (groups 1b and 2b), recovery was spontaneous; no anticholinesterase was administered.

Anaesthesia was maintained until T1/T0 was greater than 75 % and T4/T1 at least 70 %, then discontinued and the trachea extubated. The patient remained in the recovery room for at least 1 h after the end of anaesthesia, when muscle power was checked clinically by asking the patient to protrude the tongue, raise the head off the pillow for 5 s and cough [8].

The patient was visited in the ward the next day to elicit any complaints of dreaming, nausea, vomiting or discomfort and to check that all cardiovascular variables had been stable over the previous 24 h.

Data analysis

The time to 95 % depression of T1/T0, the maximum depression of T1/T0 and the time to maximum depression were noted in the two groups, as was the time for T1/T0 to recover to 5 % (when the infusion was started) and the total duration of the infusion of mivacurium. The total dose of mivacurium was also recorded, as was T1/T0 on stopping the infusion and the time from this point to T1/T0 reaching 20 % (i.e. when neostigmine was given in groups 1a and 2a).

The time for recovery of T1/T0 from 25 % to 75 % was noted with the time for T4/T1 to return to 70 %, after giving neostigmine in groups 1a and 2a or from the time when T1/T0 was 25 % in groups 1b and 2b. The pharmacodynamic data from the two groups were compared using the Mann–Whitney *U* test. The time to 5 % recovery of T1/T0 in both groups after the bolus dose of mivacurium was related to the subsequent rate of infusion of mivacurium, using a correlation coefficient.

The plasma cholinesterase activity for each patient was determined by benzoylcholine hydrolysis using an optical method [9] and the dibucaine and fluoride numbers were determined as described by Kalow and Genest [10]. The plasma cholinesterase activity in the two groups was related also to the time to 5 % recovery of T1/T0 after the bolus dose of mivacurium, using a correlation coefficient.

The plasma albumin and globulin concentrations in the two groups were compared using the Mann–Whitney *U* test.

RESULTS

There was no significant difference in the ages of the two groups, although the renal patients were of lesser weight (table I). The mean plasma albumin concentration in the renal group was significantly less than that in the healthy group, but the mean globulin concentrations in the two groups were almost identical (table I). Five renal failure patients were receiving peritoneal dialysis. The remaining patients in group 1 were receiving haemodialysis, except for male patient No. 6 (table II), who had not yet been dialysed, but was in end-stage renal failure. Four of the renal failure patients had Type 1 diabetes mellitus.

The mean cholinesterase activity (785 iu $litre^{-1}$) in group 1 was significantly different from that in group 2 (943 iu $litre^{-1}$) ($P < 0.05$). Two of the patients in group 2 and one in group 1 were atypical heterozygotes for pseudocholinesterase, with reduced dibu-

TABLE I. *Patient data and mean plasma protein concentrations of the patients in the two groups (mean (SD) [range]). ***P < 0.001 compared with group 1; no other significant differences between groups*

	Group 1 (Renal failure)	Group 2 (Healthy)
Age (yr)	42 [19–59]	45 [20–56]
Weight (kg)	63.3 (9.3) [50–81]	70.7 (9.7) [54–89]
Sex (M:F)	8:12	10:10
Albumin (g $litre^{-1}$)	34 [27–41]	42*** [32–49]
Globulin (g $litre^{-1}$)	28 [22–37]	27 [18–34]

TABLE II. *Pseudocholinesterase activity, dibucaine and fluoride numbers for each patient in the two groups. + = Atypical heterozygote; DM = diabetic; PD = peritoneal dialysis; ND = not yet dialysed*

Patient No.	Pseudocholinesterase activity (iu litre^{-1})	Dibucaine No.	Fluoride No.
Normal range	620–1370	77–83	57–67
Heterozygote		54–70	39–57
Homozygote		18–28	18–28
Group 1, female			
1	1060	85	63
2	1046	83	57
3 (DM, PD)	885	88	64
4	564	71	77
5 (PD)	694	86	56
6	946	81	67
7	1059	83	63
8	830	82	56
9	931	82	64
10	861	83	57
11 (PD)	567	89	67
12 (DM)	691	85	60
Group 1, male			
1 (DM, PD)	821	82	70
2 (DM, PD)	1082	83	56
3	533	82	56
4	856	81	61
5	623	83	59
6 (ND)	496	77	59
7 +	405	60	38
8	745	83	63
Mean (SD)	785 (207)		
Range	405–1082		
Group 2, female			
1	876	86	64
2	800	86	86
3	1010	85	53
4	977	82	54
5	1291	82	70
6	1321	86	65
7	1139	86	69
8	870	85	58
9	831	84	63
10 +	576	61	36
Group 2, male			
1	988	84	59
2	1307	84	58
3	938	82	59
4	993	82	59
5 +	747	65	50
6	1096	83	70
7	567	78	46
8	967	82	67
9	872	83	61
10	690	84	65
Mean (SD)	943 (217)		
Range	567–1321		

TABLE III. *Pharmacodynamic onset data (mean (SD)) for the two groups. ns = Not significant*

	Group 1	Group 2	P
Time to 95% depression of T1/T0 (min)	2.1 (0.77) ($n = 19$)	2.7 (0.74) ($n = 16$)	ns
Maximum depression of T1/T0 (%)	98.4 (3.5)	96.8 (4.4)	< 0.01
Time to maximum depression of T1/T0 (min)	4.1 (1.7)	4.4 (1.0)	ns

TABLE IV. *Time to 5% recovery of T1/T0 and infusion data (mean (SD) [range])*

	Group 1	Group 2	P
Time to 5% recovery of T1/T0 (min)	15.3 (6.9) ($n = 19$)	9.8 (3.5) ($n = 16$)	< 0.01
Infusion rate (µg kg^{-1} min^{-1})	6.3 (1.9)	10.4 (2.9)	< 0.001
Infusion time (min)	68 (33) [12–150]	81 (46) [40–224]	ns
T1/T0 on stopping infusion (%)	4.4 (1.8)	4.2 (1.7)	ns
Total dose of mivacurium (mg)	35.4 (13.7)	69.6 (45.3)	< 0.001

caine and fluoride numbers, and sensitivity to the drug was noted (see below). Male patient No. 7 in group 2 had a reduced cholinesterase activity and fluoride number, but normal dibucaine number. He was not sensitive to mivacurium (table II).

The maximum depression of T1/T0 after the bolus dose of mivacurium was greater in the renal failure patients ($P < 0.01$), although the times to 95% depression and maximum depression T1/T0 were not significantly different between the two groups (table III). Nineteen patients in group 1, but only 16 patients in group 2, achieved at least 95% depression of T1/T0. Only one patient (in group 1) had complete ablation of T1 (100% depression) (table III).

The renal failure patients took 1.5 times longer than the healthy patients to achieve 5% recovery of T1/T0 (15.3 *vs* 9.8 min; $P < 0.01$) (table IV). The healthy patients required a significantly greater rate of infusion of mivacurium (10.4 *vs* 6.3 µg kg^{-1} min^{-1}; $P < 0.001$) to maintain the same degree of neuromuscular block and therefore received a significantly greater total dose of the drug (table IV). There was no significant difference in the duration of infusion given in the two groups, although the mean dose and range were greater in group 2. T1/T0 when the mivacurium infusion was stopped was similar in both groups.

There was no significant difference between each group or subgroup in the time for recovery of T1/T0 to 20% after stopping the infusion (table V). Neostigmine increased the rate of recovery from neuromuscular block significantly in each group (table V). There was no significant difference between groups 1a and 2a or 1b and 2b in the rate of recovery of any of these variables, except that the time for recovery of T1/T0 from 25% to 75% in the healthy patients not given neostigmine (group 2b: 7.7 min), was significantly shorter than in the renal patients allowed to recover spontaneously (group 1b: 12.2 min) ($P < 0.05$). All the healthy patients (group 2) had recovery of T1/T0 and T4/T1 to more than 90%. All the renal failure patients had greater than 80% recovery of these variables (table V).

There was a significant negative correlation between the time to 5% recovery of T1/T0 and the required mivacurium infusion rate in both groups ($r = -0.447$; $P < 0.01$) (fig. 1).

There was a significant negative correlation also between the time to 5% recovery after a bolus dose

TABLE V. *Recovery data (mean (SD)) for the two groups. Groups 1a and 2a received neostigmine 35 μg kg^{-1} when T1/T0 = 20%. Statistical significances relate to comparisons within each group*

	Group 1			Group 2		
	a	b	*P*	a	b	*P*
Time from stopping infusion to 20% recovery (min)	7.4 (4.4)	9.2 (6.0)	ns	9.0 (4.3)	7.2 (1.7)	ns
Time from 25% to 75% recovery of T1/T0 (min)	5.6 (2.8)	12.2 (8.2)	< 0.01	4.7 (2.3)	7.7 (1.2)	< 0.001
Time to 70% recovery of T4/T1 (min)	5.7 (2.6)	13.7 (4.5)	< 0.01	7.6 (3.8)	12.5 (2.7)	< 0.05

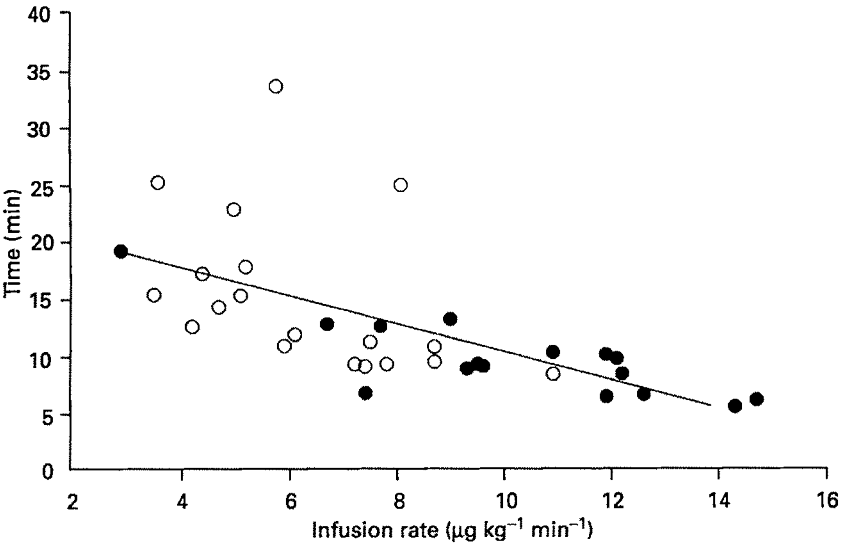

FIG. 1. The time to 5% recovery of T1/T0 plotted against the infusion rate of mivacurium for all the patients in the two groups who developed greater than 95% depression of T1/T0. ○ = Renal patients; ● = healthy patients. There was a significant correlation between these variables overall ($r = -0.447$; $P < 0.01$).

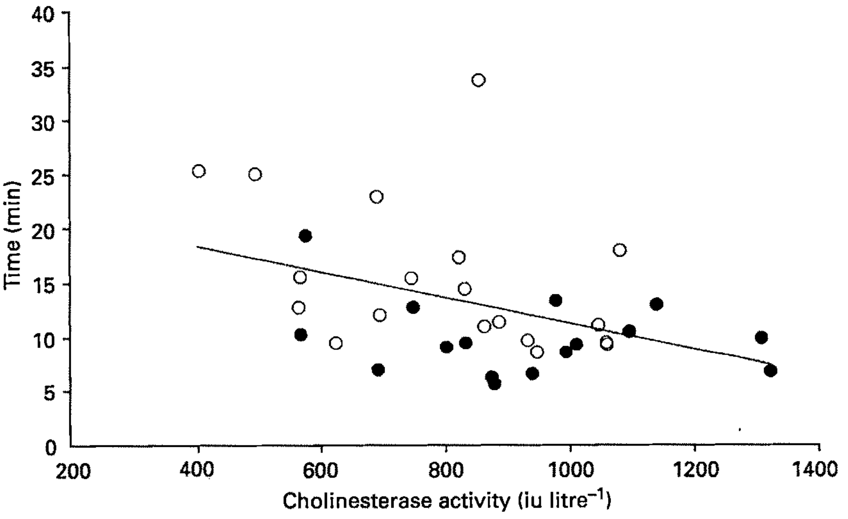

FIG. 2. The time to 5% recovery of T1/T0 plotted against the plasma cholinesterase activity in each of the patients in the two groups who developed greater than 95% depression of T1/T0. ○ = Renal patients; ● = healthy patients. There was a significant correlation between these variables overall ($r = -0.42$; $P < 0.02$).

TABLE VI. *Prolonged recovery indices in the three patients with atypical cholinesterase. Pseudo. = Pseudocholinesterase; D = dibucaine number; F = fluoride number; N = neostigmine*

	Pseudo. activity	D	F	Time to 5% recovery of T1/T0 (min)	Mivacurium infusion rate ($\mu g\ kg^{-1}\ min^{-1}$)	Time to 20% recovery of T1/T0 (min)	Time from 25% to 75% recovery of T1/T0 (min)
Group 1							
Male, No. 7	405	60	38	25.3	3.6	12.1	13.5
Group 2							
Male, No. 5	747	65	50	12.7	7.7	8.7	4.6 (N)
Female, No. 10	576	61	36	19.3	2.9	8.1	7.7

TABLE VII. *Mean* (SD) *cardiovascular variables after the bolus dose of mivacurium in each group. Tracheal intubation was attempted after the 2-min recording*

Time (min)	Mean arterial pressure (mm Hg)		Heart rate (beat min^{-1})	
	Group 1	Group 2	Group 1	Group 2
0	80.8 (14.5)	82.1 (11.9)	72.1 (16.7)	72.1 (10.5)
1	77.8 (12.6)	80.1 (12.1)	70.5 (16.7)	71.0 (11.1)
2	78.2 (10.9)	79.3 (9.4)	70.7 (17.6)	73.3 (10.4)
3	87.5 (19.1)	97.0 (10.6)	80.4 (17.7)	83.3 (9.1)
4	91.3 (21.6)	101.9 (13.4)	80.1 (17.7)	87.7 (10.8)
5	89.1 (19.7)	97.9 (14.2)	77.5 (17.2)	85.8 (12.4)

TABLE VIII. *Conditions for tracheal intubation. *Anatomically difficult—intubated at 7 min*

	Excellent	Good	Poor	Impossible
Group 1				
2 min	7	8	1	4
3 min	2	2	—	—
Group 2				
2 min	4	7	1	8
3 min	1	3	3	1*

of mivacurium and the plasma cholinesterase activity for each patient ($r = -0.42$; $P < 0.02$) (fig. 2).

The pharmacodynamic data for the three patients (two healthy) with abnormal dibucaine and fluoride numbers is given individually in table VI. Two of these patients (group 1: male No. 7; group 2: female No. 10) were particularly sensitive to the drug, with a prolonged time to 5% recovery of T1/T0 and a reduced infusion rate of mivacurium. The third patient (group 2: male No. 5), whose cholinesterase activity was at the lower end of the normal range, had a slightly longer time to 5% recovery of T1/T0 and required a slightly reduced infusion rate of mivacurium. Because the mivacurium infusion was adjusted according to the value of T1/T0, the subsequent recovery times were within the normal range.

Cardiovascular variables. The mean heart rate and arterial pressure recordings immediately before and for 1-min intervals up to 5 min after the bolus dose of mivacurium in groups 1 and 2 are given in table VII. Tracheal intubation was performed after the 2-min recording. At this dosage, mivacurium did not have a significant cardiovascular effect. Mean arterial pressure and heart rate increased after tracheal intubation.

Erythema was noted at the injection site, spreading up the forearm to the necklace area, in 16 of the healthy patients and in three of the renal group. It was not associated with any significant cardiovascular changes.

Tracheal intubation. In 60% of the healthy patients and 80% of the renal patients, the trachea was intubated satisfactorily at 2 min. In only one patient was intubation impossible after 3 min, because of anatomical difficulties. The trachea was intubated eventually at 7 min (table VIII).

There were no clinical problems of recurarization in the recovery room after anaesthesia.

All the patients were interviewed the next day in the ward. All were satisfied with their anaesthetic; none had any recall of dreaming or awareness, or any evidence of recurarization. There were no complaints of nausea or vomiting and all had stable cardiovascular recordings.

DISCUSSION

Mivacurium chloride has a time to onset of action similar to those of atracurium and vecuronium: a dose of twice the ED_{95} produced 95% depression of T1/T0 in 162 s in healthy patients (table III) compared with 110 s and 177 s, respectively, for the older agents [11]. In this study, renal failure patients had a similar, possibly shorter, time to maximum depression of T1/T0 (table III), but in the earlier study of atracurium and vecuronium by Hunter, Jones and Utting, an anephric group had a longer time to maximum block [11]. This was thought to be caused by slower circulation times in these ill patients. If mivacurium is metabolized by pseudocholinesterase, the more rapid onset in renal patients may possibly be explained by a decreased plasma cholinesterase activity in this group. Delivery of blocking agent to the neuromuscular junction is of prime importance in this respect [12]; a reduced plasma metabolism may thus increase the amount of drug delivered to the site of action in the time immediately after a bolus has been given. Compared with suxamethonium, however, the onset time was still slow and mivacurium is unlikely to replace the older drug for rapid tracheal intubation. The trachea of renal patients may be intubated at 2 min, but in healthy patients it may be necessary to wait for 3 min if a bolus dose of only $2 \times ED_{95}$ has been used.

The return of T1/T0 to 5% in a mean time of 10 min (table IV) in healthy patients indicates that mivacurium may be useful in short procedures such as laparoscopy, bronchoscopy and tonsillectomy, where even vecuronium and atracurium may be too long-acting. If this drug is mainly metabolized in man by plasma cholinesterase, however, it may have the same disadvantage as suxamethonium: unexpected yet marked sensitivity to mivacurium may occasionally be encountered. As this study has confirmed (table VI), atypical heterozygotes for pseudocholinesterase are not uncommon in the Caucasian population, with an incidence of about 4%. The findings reported here substantiate those reported first by Ostergaard and colleagues, who also demonstrated marked sensitivity to mivacurium in this atypical population [13], although it should be added that other workers have reported a normal response in a patient with atypical cholinesterase [14].

The less marked, but nevertheless significantly decreased, requirement for mivacurium in chronic renal patients was not a result of genetic abnormality in all but one of the patients reported here, but may be explained by an acquired decrease in plasma cholinesterase activity. The mean plasma cholinesterase activity was significantly less in the renal patients and, perhaps more importantly, the time to 5% recovery of T1/T0 was correlated negatively with cholinesterase activity ($P < 0.02$) (fig. 2). Thus the less the cholinesterase activity, the longer the time to recovery from a bolus dose. These results are very suggestive that this is the cause of sensitivity to mivacurium in patients with renal failure.

The cause of a low cholinesterase activity in these patients is unclear, but its existence is well recognized. The possibility that it is a result of traumatic damage to the enzyme during haemodialysis has been refuted [15] and would not explain the sensitivity seen also in peritoneal dialysis patients. All the patients reported here had normal liver function tests, so it is unlikely that synthesis of the enzyme was impaired.

Another possible cause of the sensitivity of chronic renal failure patients to mivacurium may be decreased plasma protein binding. The degree of binding of mivacurium is unknown, but neuromuscular blocking agents are thought to bind more to globulin than albumin [16]. The mean globulin concentrations in the two groups were similar in this study, and thus altered plasma protein binding is unlikely to explain these findings.

This study was designed to eliminate any influence of renal excretion in the renal failure group, by avoiding the study of patients undergoing anaesthesia for renal transplantation. Thus it may well be that the cause of the difference in the two groups is in part a result of lack of renal excretion of the drug. Pharmacokinetic studies would be needed to confirm this conclusively.

The infusion requirements in the healthy patients during balanced anaesthesia ($10.4\ \mu g\ kg^{-1}\ min^{-1}$) would appear to be greater than those reported by other workers using similar anaesthetic techniques in adults, although different methods of neuromuscular monitoring were used. Ali and colleagues [1], using mechanomyography, reported mivacurium dose requirements of $8.3\ \mu g\ kg^{-1}\ min^{-1}$ and Brandom and colleagues used doses of mivacurium $7.9\ \mu g\ kg^{-1}\ min^{-1}$ to maintain T1/T0 at 5%, using a Relaxograph to monitor neuromuscular function [17]. In children, also, it would seem that greater infusion doses, comparable to those in this study, are required [18].

It has already been demonstrated that an anticholinesterase only hastens by a few minutes the recovery rate after bolus doses or infusions of mivacurium [2, 17, 19] and this work supports the earlier findings. In the renal failure patients, spontaneous recovery of T1/T0 was slower than in healthy patients, however (table V), and the use of neostigmine probably is indicated in this group.

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GASTRODUODENAL DYSFUNCTION AS A CAUSE OF GASTRIC BACTERIAL OVERGROWTH IN PATIENTS UNDERGOING MECHANICAL VENTILATION OF THE LUNGS

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SUMMARY

We have studied 15 patients undergoing mechanical ventilation of the lungs for evidence of a relationship between gastroduodenal dysfunction and gastric bacterial overgrowth. Duodenal reflux was detected by quantitative measurement of conjugated bilirubin in gastric aspirate specimens. The pH and bacterial content of these specimens were analysed. A minority of specimens with pH $<$ 3.5 contained measurable numbers of viable bacteria. The total bacterial count and the count of Gram negative bacteria correlated significantly with specimen pH in both cases ($P < 0.001$, in both). In the 72 specimens of gastric aspirate with pH $>$ 3.5, the presence of Gram negative bacteria was associated significantly with detectable bilirubin ($P <$ 0.001). The total bacterial count was greater also in specimens containing bilirubin ($P = 0.009$). These results suggest that gastroduodenal dysfunction may promote gastric bacterial overgrowth, contributing to the development of ventilator-associated pneumonia.

KEY WORDS

Gastrointestinal tract: gastric bacterial overgrowth. Intensive care: mechanical ventilation.

Gastric bacterial overgrowth is an important factor in the pathogenesis of ventilator-associated pneumonia. Bacteria isolated from the lower respiratory tract of patients undergoing ventilation were recovered also from stomach contents in the majority of subjects [1]. It has been shown also that patients with an increased gastric pH, caused by administration of either antacid or histamine receptor antagonists for stress ulcer prophylaxis, are more likely to develop gastric bacterial overgrowth [2]. Furthermore, in a prospective investigation of risk factors of ventilator-associated pneumonia, an association has been demonstrated between the development of pneumonia and the use of cimetidine for stress ulcer prophylaxis [3]. Studies implicating increased gastric pH as a contributory factor in gastric bacterial overgrowth and subsequent pneumonia have been reviewed recently [4].

Other changes in gastric physiology do not appear to have been considered as potential contributory factors in gastric bacterial overgrowth. The present study aimed to investigate the relationship between gastroduodenal reflux and gastric bacterial overgrowth.

PATIENTS AND METHODS

We studied consecutive patients admitted to a general Intensive Care Unit. Only patients with both a tracheal tube and a nasogastric tube *in situ* at or shortly after admission were included. Patients who had had recent gastrointestinal or thoracic surgery were excluded. Patients' relatives were asked for informed consent before a patient was entered in the study, which was approved by the District Research Ethics Committee.

Samples of gastric contents were taken soon after admission to the ICU and regularly thereafter, until tracheal or nasogastric extubation. The first 5-ml aspirate was discarded (to allow for deadspace in the nasogastric tube) before collection of each sample into a fresh, sterile 20-ml syringe. The position of the tip of the nasogastric tube was checked by examination of daily chest radiographs.

Gastric aspirate specimens were transported to the laboratory for analysis immediately after collection, or stored at 4 °C until they could be transported. Recordings of pH were made with a temperature-corrected, microprocessor pH electrode reading to an accuracy of ±0.02 pH units (model 3037, Jenway Ltd, Dunmow, Essex).

Conjugated bilirubin was measured in gastric aspirates using a colorimetric method [5], and a spectrophotometer (Cambridge Scientific). A calibration curve was drawn using a five-point series of standard dilutions of analytical grade bilirubin (Sigma), with five replicate assays at each point. Two replicate assays were performed on each specimen of gastric aspirate.

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TABLE I. *Clinical data and first gastric sampling times for patients studied*

Patient No.	Age (yr)	Sex	Time to first aspirate (h)	Diagnosis on admission	APACHE score
1	66	F	13	Respiratory arrest, pneumonia	18
2	74	M	18	Respiratory failure	23
3	69	F	15	Sternotomy, respiratory failure, pneumonia	16
4	21	M	12	Head injury	24
5	19	M	48	Head injury, multiple fractures	22
6	25	M	29	Head injury	26
7	20	M	59	Head injury	19
8	55	F	11	Encephalitis	16
9	59	M	16	Abdominal injury	12
10	24	M	45	Respiratory failure, aplastic anaemia	14
11	71	M	15	Repair aortic aneurysm	12
12	43	M	31	Chest injury	12
13	62	M	21	Head injury	23
14	90	F	16	Head and facial injury	33
15	20	M	31	Head injury	16

TABLE II. *Gastrointestinal and antibiotic agents used in the patients studied*

Patient No.	Stress ulcer prophylaxis	Other gastric agents	Antibiotics at ICU admission	Subsequent antibiotics
1	Ranitidine	Antacid	Cefotaxime Metronidazole Benzyl penicillin	Erythromycin
2	Sucralfate	Antacid Metoclopramide	Ampicillin Erythromycin	—
3	—	—	Ampicillin	Cephradine
4	—	Antacid	Sulphadimidine Benzyl penicillin	Ampiclox
5	Sucralfate	—	Cephradine	—
6	Sucralfate	—	Sulphadimidine Benzyl penicillin	—
7	Sucralfate Ranitidine	Cisapride	Sulphadimidine Benzyl penicillin Flucloxacillin	Ampicillin Cefotaxime
8	Sucralfate	—	Benzyl penicillin	Flucloxacillin Ampicillin
9	Sucralfate	—	Cephradine Metronidazole	—
10	Ranitidine	Metoclopramide	Gentamicin Piperacillin	Cefotaxime
11	Ranitidine	—	Cephradine Metronidazole	—
12	Ranitidine	Metoclopramide	Cefuroxime	Ampicillin Gentamicin
13	—	Antacid	Sulphadimidine Benzyl penicillin	—
14	—	—	Cephradine Metronidazole	—
15	Ranitidine	—	Sulphadimidine Benzyl penicillin	Ampicillin Flucloxacillin

Aliquots of gastric contents were spread on a single heated blood agar plate (5% horse erythrocytes, Blood Agar Base No. 2, Oxoid) and a single MacConkey agar plate (Oxoid) using a spiral plating device (Don Whitley, Shipley) [6]. Three 10-fold dilutions of gastric aspirate were prepared in sterile phosphate-buffered saline and the above plating procedure repeated. After overnight incubation in air at 37 °C, agar plates were examined using a counting template and an electronic colony counter (Gallenkamp). Colony counts for all bacteria and Gram negative bacilli were converted to $\log_{10}$ viable counts using standard tables.

Statistical analysis was performed by computer using C-stat version 1.0 (Cherwell Scientific, Oxford) running on an IBM compatible microcomputer (Amstrad 1640, 40 Mb hard drive).

RESULTS

Clinical details of patients studied are shown in table I and therapeutic agents used are listed in table II.

A minority of gastric aspirates with pH < 3.5 were found to contain measurable numbers of bacteria (fig. 1) or Gram negative bacilli (fig. 2). Greater counts of all bacteria and of Gram negative bacilli were found in specimens with a greater pH, and in both cases a positive correlation was found between bacterial count and specimen pH ($P < 0.001$ in both cases).

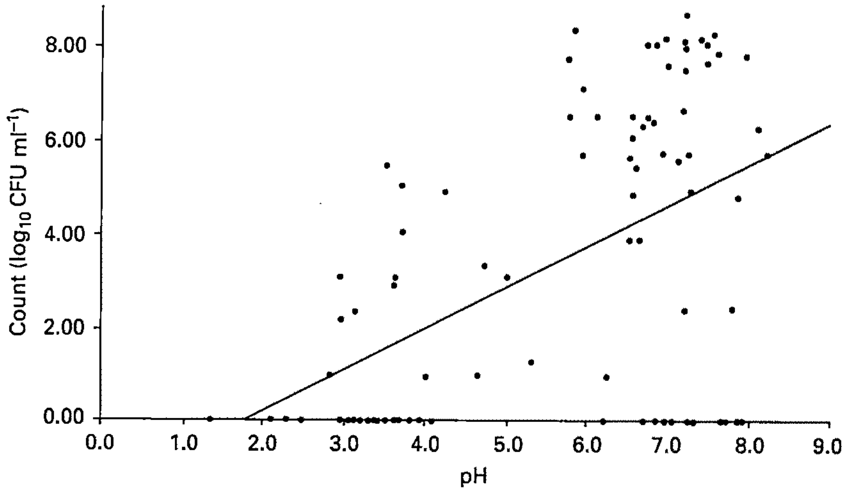

FIG. 1. Total bacterial count *vs* pH of all gastric aspirate specimens obtained (regression line: $y = 0.86x - 1.477$; $r = 0.5438$; $P < 0.001$). CFU = Colony forming units.

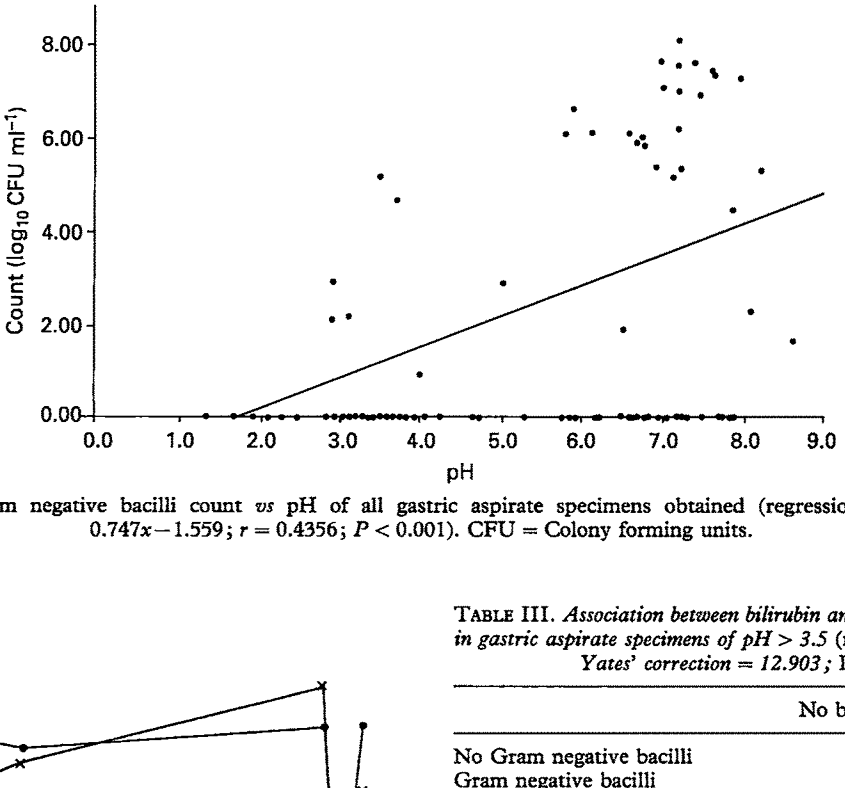

FIG. 2. Gram negative bacilli count *vs* pH of all gastric aspirate specimens obtained (regression line: $y = 0.747x - 1.559$; $r = 0.4356$; $P < 0.001$). CFU = Colony forming units.

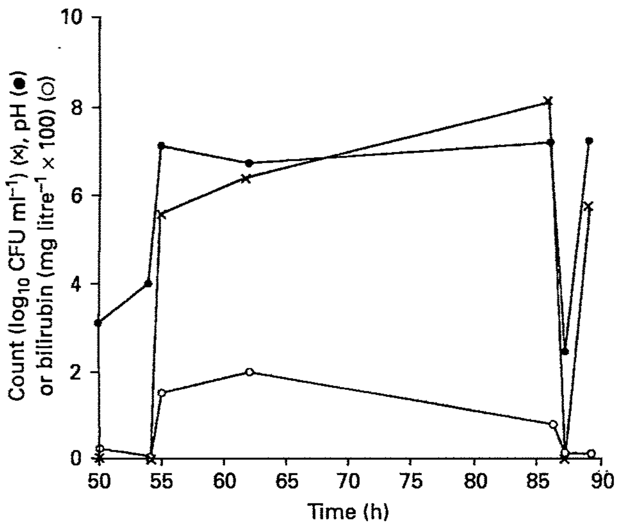

FIG. 3. Bacterial count (Gram negative bacilli), pH and bilirubin in gastric aspirate specimens from patient 1, showing changes over the last 40 h studied. CFU = Colony forming units.

TABLE III. *Association between bilirubin and Gram negative bacilli in gastric aspirate specimens of pH > 3.5* (n = *72*; *chi-square with Yates' correction* = *12.903*; P < *0.001*)

	No bilirubin	Bilirubin
No Gram negative bacilli	31	6
Gram negative bacilli	14	21

Gastric bilirubin concentrations were found to vary with time. In some patients, Gram negative bacteria appeared to be associated with the presence of bilirubin in the gastric aspirate, as illustrated in figure 3, which depicts changes in the gastric aspirate from patient No. 1 over the final 40 h of nasogastric intubation. The count of Gram negative bacteria increased sharply from undetectable after the pH increased, but at the same time as an increase in bilirubin concentration. The Gram negative bacterial count continued to increase slowly while the pH remained greater than 3.0 units, but declined sharply when the pH decreased to less than this.

Chi-square analysis of gastric aspirates with pH > 3.5 from all patients showed a significant association between the presence of bilirubin and Gram negative bacilli (table III).

A Mann–Whitney *U* test of bacterial count in specimens with and without bilirubin (fig. 4) re-

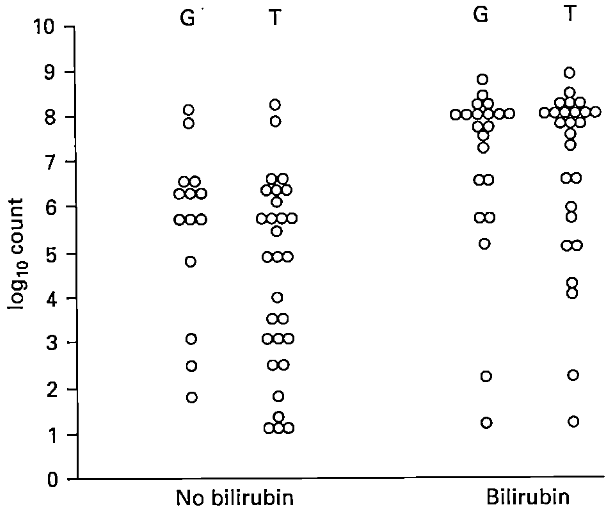

FIG. 4. Association between greater total bacterial count (T), greater Gram negative count (G) and presence of bilirubin in gastric aspirate specimens of pH > 3.5. Mann–Whitney *U* test: total bacteria in bilirubin-containing specimens *vs* total in bilirubin free specimens—$n_1 = 23$, $n_2 = 28$, $U = 117$, $P = 0.009$; Gram negative bacterial count in bilirubin-containing specimens *vs* count in bilirubin-free specimens—$n_1 = 19$, $n_2 = 14$, ns.

vealed that total bacterial count was significantly greater in specimens containing conjugated bilirubin ($P = 0.009$).

DISCUSSION

There are probably several major determinant factors of gastric bacterial overgrowth in patients undergoing mechanical ventilation of the lungs. Recent work has focused attention on the role of gastric pH. While the relationship between increased gastric pH and bacterial count is supported by the findings of this study, an increased intragastric pH cannot be the sole explanation for gastric bacterial overgrowth. Given the appropriate nutrients and a source of bacteria, an increased pH would be expected to do little more than permit bacterial growth.

Until now, there has been speculation about possible sources for bacteria in the stomach lumen of patients undergoing ventilation, but no previous investigation has identified their origin. The association observed between intragastric Gram negative bacteria and duodenogastric reflux in these patients provides evidence to support an intestinal source for these bacteria.

In normal individuals, the duodenum contains very few bacteria and no Gram negative bacilli, but Gram negative species may be present in large numbers after contamination with bacteria from further down the small intestine, such as may occur after gastrointestinal surgery or during opioid analgesia [7]. A greater gastric pH caused by the reflux of duodenal contents might have an additional promoting effect on the growth of bacteria introduced to the stomach by this route.

Gastroduodenal reflux is known to occur intermittently in normal individuals [8] and it is possible that the loss of gastric pacemaker dominance caused by the altered gastric emptying in these patients would increase both active and passive duodenal reflux. Evidence has been presented for impaired gastric emptying in head injury patients [9]. It is possible that the failure of this study to achieve statistical significance may be explained by its small size and a possible range of gastric emptying patterns. Further studies are required to clarify this issue.

The results of the present study suggest that gastric bacterial overgrowth is promoted by duodenal reflux in patients undergoing mechanical ventilation of the lungs. Duodenal reflux should be considered with increased intragastric pH as a potential risk factor for ventilator-associated pneumonia and addressed in future studies. These, and other aspects of gastroduodenal dysfunction might be investigated as possible determinants of bacterial colonization of the ventilated lung.

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EFFECT OF LOW AND HIGH CONCENTRATIONS OF ALFENTANIL ADMINISTERED INTRATHECALLY ON Aδ AND C FIBRE MEDIATED SOMATOSYMPATHETIC REFLEXES

C. WANG, M. K. CHAKRABARTI AND J. G. WHITWAM

SUMMARY

We have studied the effects of alfentanil administered intrathecally on somatosympathetic reflexes evoked by stimulation of radial and tibial nerves in 10 anaesthetized and paralysed dogs. In five animals, alfentanil was administered in doses of 100, 100, 200 and 400 μg in 0.8 ml and 800 μg in 1.6 ml prepared from the formulation of 500 μg ml^{-1}. Five others received alfentanil (high concentration formulation, 5 mg ml^{-1}) in doses of 500 and 2000 μg in 0.5 ml and 5000 μg in 1 ml. C fibre tibial nerve reflexes were depressed by 100 μg and abolished with doses of 200–400 μg, but the Aδ response remained unaffected. Aδ responses were depressed also and abolished, respectively, by doses of alfentanil 2000 μg and 5000 μg. At the larger, but not the smaller, concentration there was evidence of baroreflex sensitization probably caused by systemic absorption of the drug.

KEY WORDS

Anaesthetic techniques: spinal. Analgesics: alfentanil. Nerve: axon, conduction, transmission. Reflexes: spinal, baroreceptor.

It is well known that nociceptive stimulation of afferent somatic sensory nerves induces changes in arterial pressure mediated by autonomic reflexes [1]. The sympathetic nervous system response to a single supramaximal somatic stimulus consists of two bursts of activity which may be recorded in sympathetic nerves and are a result of stimulation of afferent Aδ and C fibre pathways, respectively; differences in reflex times depend on the different conduction velocities along the afferent pathway [1, 2].

Previous studies have demonstrated that, in many reflex systems, the C fibre evoked response shows a greater sensitivity to depression by opioids than the Aδ response [3–8]. However, in most of these studies the opioids were administered systemically, which may result in antinociceptive activity through both supraspinal and spinal mechanisms. Typically localized pain (for example, pinprick) is affected less by opioids than more diffuse pain from less localized stimuli (for example, a heat stimulus), which are sometimes referred to "first" or "fast" pain and "second" or "slow" pain and which are regarded traditionally as being mediated by afferent Aδ and C fibre pathways [9–11].

The dose of alfentanil, administered systemically, required to abolish the Aδ responses is 10–12 times that for C reflexes [12], which is the widest margin for any of the opioids tested to date. The present study was undertaken to determine if the Aδ reflexes also show a similar reduction in sensitivity to the intrathecally administered drug compared with the C reflexes.

MATERIALS AND METHODS

Ten greyhound dogs of both sexes, weighing 22–30 kg, were studied (Home Office Licence No PPL 70/01654). Anaesthesia was induced with a single dose of methohexitone 10–15 mg kg^{-1} i.v. and maintained with alpha-chloralose (1% solution) in an initial bolus dose of 30 mg kg^{-1} followed by a continuous infusion of 17–20 mg kg^{-1} h^{-1}. The lungs were ventilated mechanically (Harvard pump) via a tracheal tube with oxygen enriched air. Muscle paralysis was maintained with suxamethonium 10 mg i.v. which was effective for approximately 30 min. The depth of anaesthesia of the animal was observed before each dose of suxamethonium (immobility, floppy ears and absent responses to glabellar tap and cutaneous stimulation). The left femoral artery and vein were catheterized for arterial pressure recording, blood sampling, drug administration and fluid infusion. Arterial pH, Pa_{CO_2}, Pa_{O_2} and oesophageal temperature were maintained in the ranges 7.30–7.35, 4.5–5.5 kPa, 20–27 kPa, and 37–39 °C, respectively.

Laminectomy was performed at L2–3 and the dura mater exposed and cannulated (22-gauge Y-Can, Wallace) for intrathecal injection of drug. A lateral superficial branch of the radial and of the tibial nerve were exposed in the left foreleg and right hindleg, and single fascicles of the renal sympathetic nerves were exposed retroperitoneally close to the renal artery. All nerves were desheathed at the stimulation or recording sites, cut distally and mounted on silver–silver chloride electrodes in a pool of mineral oil. Throughout these studies, the animal was maintained in a head-up tilt of 15° to reduce ascending spread of intrathecal drugs.

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Supramaximal electrical stimuli (duration 0.5 ms; intensity 30 V; frequency 0.33 Hz) were applied to the peripheral nerves using a Grass S88 Stimulator with a matched, directly coupled isolation unit (Grass 478A). Efferent activity in renal sympathetic nerves was processed via a preamplifier (Tektronix type 122) and displayed on a dual beam oscilloscope (Tektronix type 565). Sixteen evoked responses from the renal sympathetic nerves were averaged using a Neurolog system (NL 750 Digitimer) and the averages rectified and integrated (Neurolog NL90). The rectified and integrated signals were displayed on a Devices MX2 pen recorder. A Gould system (Gould 1602) was used to measure the total electrical activity of this rectified, integrated signal, which was recorded in arbitrary units and changes expressed as a percentage of the control value. The arterial pressure was measured using calibrated strain gauges and was displayed together with beat-by-beat heart rate using a heated stylus recording system (Devices M19). After control data were set up and recorded, during each experimental sequence no adjustments were made to either the preparation or the instrumentation.

After the surgical procedures, the preparation was allowed to stabilize for at least 30 min. Control averaged evoked responses in the renal sympathetic nerve were obtained in response to tibial and radial nerve stimulation. Resting mean arterial pressure (MAP) and heart rate (HR) were recorded also.

Five animals were given alfentanil intrathecally (i.t.) in incremental doses of 100, 100, 200 and 400 µg in 0.8 ml and, finally, 800 µg in 1.6 ml (total volume 4.8 ml) at intervals of 10 min. These doses were made up from the standard formulation of alfentanil (500 µg ml^{-1}) diluted with physiological saline when necessary. Five other animals were given greater concentrations of alfentanil, prepared from the formulation containing alfentanil 5 mg ml^{-1}, at intervals of 15 min: doses of 500 and 2000 µg were administered in volumes of 0.5 ml by diluting the formulation with physiological saline; the final dose of 5000 µg was administered in 1 ml of the undiluted formulation. In all preparations 20 min after the final dose of alfentanil, naloxone 2 mg was administered i.v. After all measurements and recordings were completed, 1 % lignocaine 1 ml was administered i.t. to demonstrate abolition of peripheral evoked reflexes in renal sympathetic nerve and hence the correct placement of the intrathecal cannula.

Averaged evoked responses in renal sympathetic nerves were recorded, starting 5 min after each drug injection. From four to eight stimuli were required for full activation of the C reflex, after which 16 responses were averaged.

Resting MAP and HR were recorded throughout each experiment.

Analysis of variance and paired *t* tests were used for statistical comparison.

RESULTS

The effects of alfentanil in small and large concentrations on tibial and radial evoked somatosympathetic reflexes from one animal in each group are illustrated in figures 1 and 2. The mean processed data of responses evoked by tibial nerve stimulation from five animals in each group are shown in figures 3 and 4.

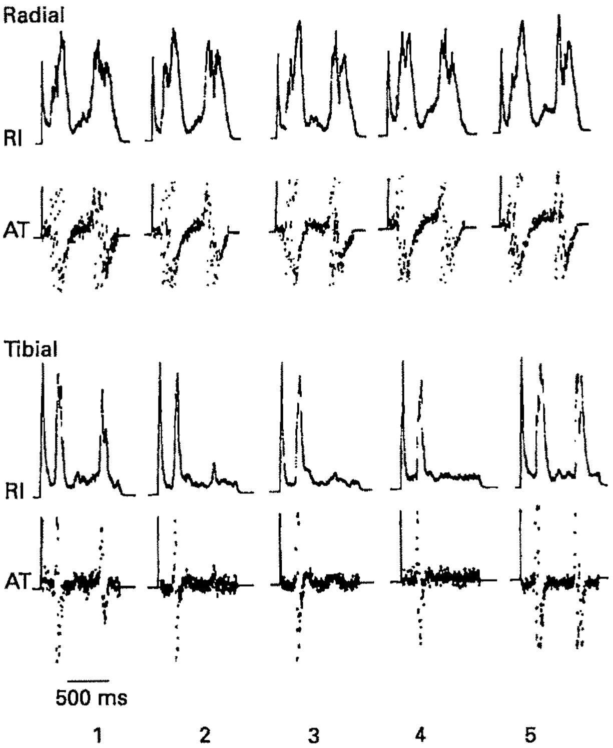

FIG. 1. Effects of the smaller concentration of alfentanil i.t. and naloxone 2 mg i.v. on the radial and tibial evoked reflexes in renal sympathetic nerves in one animal. Upper traces: rectified integral (RI) of the averaged signal of the responses; lower traces: averaged transients (AT) of 16 responses. 1 = Control; 2 = 5 min after alfentanil total dose 100 µg (in 0.8 ml); 3 = 5 min after alfentanil total dose 200 µg (in 1.6 ml); 4 = 5 min after alfentanil total dose 1600 µg (in 4.8 ml); 5 = 5 min after naloxone 2 mg i.v.

Small concentration of alfentanil (500 µg ml^{-1})

It may be seen in figure 1 that the C fibre response to tibial nerve stimulation was virtually abolished by alfentanil 100 µg i.t. However, at this dose the mean of the C fibre responses was reduced to 40 % in the five animals (fig. 3). Doses of alfentanil between 200 and 400 µg completely abolished these responses. In contrast, the Aδ response was not affected by a dose of 800 µg in 1.6 ml of the undiluted formulation (a cumulative dose of 1600 µg and a total volume of alfentanil solution of 4.8 ml) (fig. 3).

There were no significant changes in Aδ and C reflexes from radial nerve stimulation throughout (fig. 1), indicating absence of a significant supraspinal component in the effect of the drug on the response to tibial nerve stimulation.

Large concentration of alfentanil (5000 µg ml^{-1})

A single dose of alfentanil 500 µg in 0.5 ml of solution (1000 µg ml^{-1} concentration) eliminated the C reflexes (figs 2, 4), with only a small reduction in the Aδ responses to tibial nerve stimulation. In the preparation illustrated in figure 2, an additional 2000 µg in 0.5 ml of solution (cumulative dose of 2500 µg in 1 ml of solution) caused a major reduction in the Aδ response, with a mean reduction of 30 % in

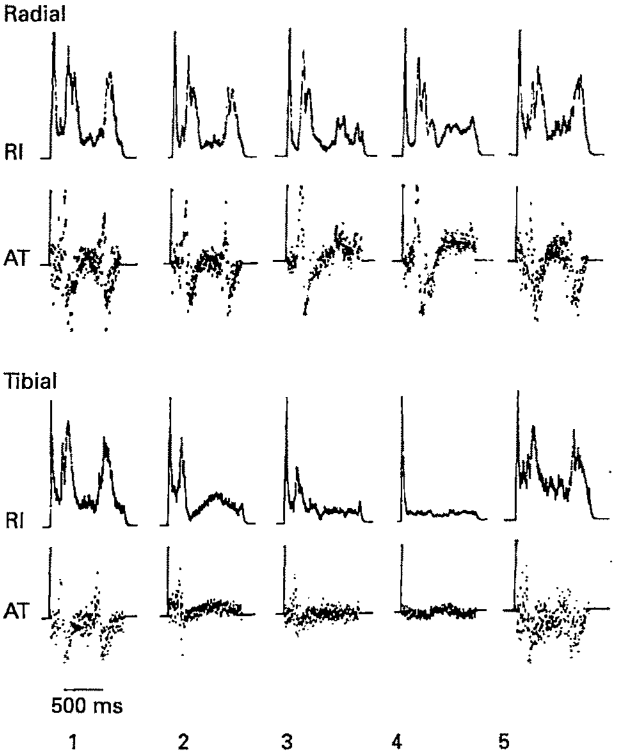

FIG. 2. Effects of the greater concentration of alfentanil i.t. and naloxone 2 mg i.v. on the radial and tibial nerve evoked reflexes in renal sympathetic nerves in one animal. Upper traces: rectified integral (RI) of averaged signals; lower traces: averaged transients (AT) of 16 responses. 1 = Control; 2 = 5 min after alfentanil 500 μg in 0.5 ml; 3 = 5 min after a second dose of alfentanil 2000 μg in 0.5 ml (total dose of 2500 μg in 1 ml); 4 = 5 min after third dose of alfentanil 5000 μg in 1 ml (total dose 7500 μg in 2 ml); 5 = 5 min after naloxone 2 mg i.v.

the five animals (fig. 4). A further increment of alfentanil 5000 μg in the undiluted formulation (1 ml) abolished the Aδ reflexes (figs 2, 4)—a cumulative dose of 7500 μg in a total volume of 2 ml.

For radial nerve stimulation, there were no significant changes in the Aδ responses throughout. However, the mean C fibre response was reduced to 75 % of control after the second dose of alfentanil (a total dose of 2500 μg in 1 ml) and it was abolished totally after the third dose (cumulative dose of 7500 μg in 2 ml of solution) (figs 2, 4).

Naloxone 2 mg i.v.

The effects of alfentanil were antagonized completely by naloxone 2 mg i.v., the responses returning to values not significantly different from control, indicating absence of damage to the spinal cord.

Cardiovascular changes

There were only minimal changes in MAP and HR in those animals receiving the smaller concentration of alfentanil. In contrast, in those receiving the greater concentration, there was clear evidence of baroreflex sensitization, with reductions in both heart rate and systemic arterial pressure. It may be seen in figure 5 that, while the mean MAP in these animals decreased from a control value of 169 mm Hg to 144 mm Hg after 500 μg ($P < 0.05$), and to approximately 115 mm Hg after cumulative doses of 2500 μg and 7500 μg, the HR declined from a mean control value of 185 beat min^{-1} to 148 beat min^{-1} ($P < 0.05$), 74 beat min^{-1} and 68 beat min^{-1} ($P < 0.01$) after the first, second and third doses, respectively.

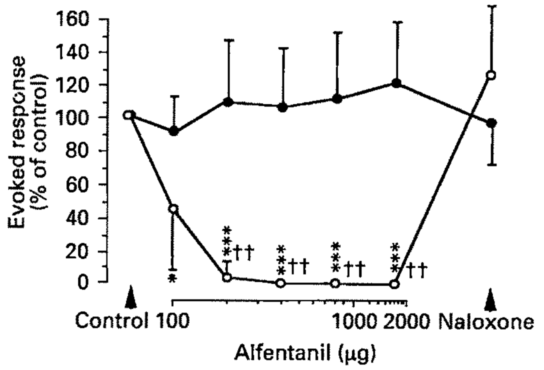

FIG. 3. Effect of small concentrations of alfentanil administered i.t. on the Aδ (●) and C (○) reflexes evoked in renal sympathetic nerve by stimulation of the tibial nerve. Relative changes in integrated electrical activity of the averaged transient of 16 responses in five animals (expressed as percent of control) (mean, SD). Doses of alfentanil 100, 200, 400, 800 and 1600 μg i.t. are shown as cumulative dose (total volume of solution 4.8 ml) on a logarithmic scale. Naloxone dose was 2 mg i.v. Significant differences: $^{*}P < 0.05$, $^{***}P < 0.001$—Aδ and C fibre mediated responses compared with control; $^{††}P < 0.01$—C reflexes compared with Aδ.

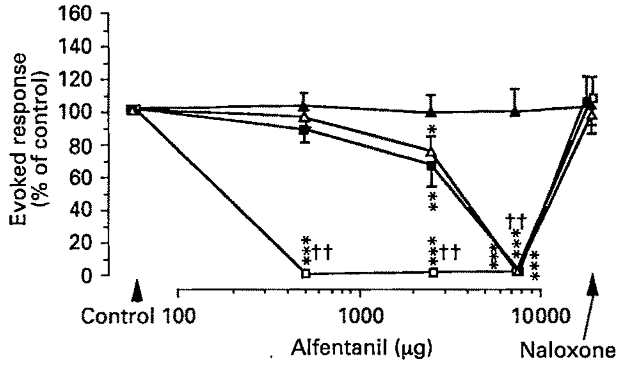

FIG. 4. Effect of large concentrations of alfentanil i.t. on the responses in renal sympathetic nerve, evoked by stimulation of tibial nerve (■ = Aδ reflexes; □ = C reflexes) and radial nerve (▲ = Aδ reflexes; △ = C reflexes). Relative changes in integrated electrical activity of the averaged transient of 16 responses in five animals (expressed as percent of control) (mean, SD). Doses of alfentanil 500, 2500 and 7500 μg i.t. are shown on a logarithmic scale as the cumulative dose (total cumulative volume of solution 2 ml). Naloxone dose was 2 mg i.v. Significant differences: $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$—Aδ and C fibre mediated responses compared with control; $^{††}P < 0.01$—C reflexes compared with Aδ.

DISCUSSION

This study has shown that relatively small doses of alfentanil, in the range 200–400 μg injected i.t. in the lumbar region, abolished C fibre but not Aδ sympathetic reflex responses to stimulation of tibial nerve in the dog. This suggests that the analgesic properties of this drug injected in an accepted dose of approximately 100 μg i.t. in man in a low concentration may also be attributed principally to depression of C reflexes [13]. Increasing the concentration of alfentanil from 125 μg ml^{-1} to 500 μg ml^{-1} and the injected volume to 4.8 ml (which is a large volume in the dog) did not abolish the tibial

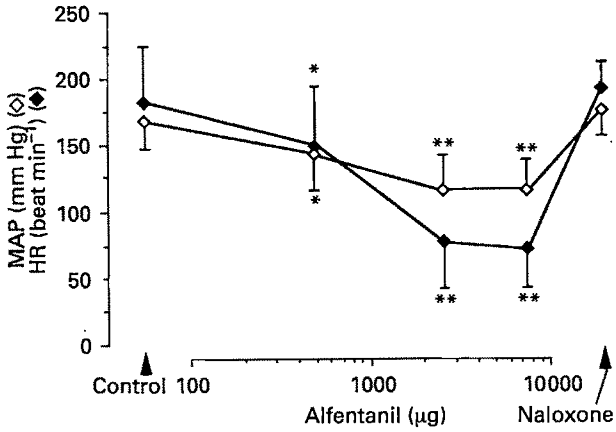

FIG. 5. Cardiovascular changes during administration of the large concentration of alfentanil i.t. followed by naloxone 2 mg i.v. Cumulative dose of drug is shown on a logarithmic scale. ◇ = Mean arterial pressure (MAP); ◆ = heart rate (HR). Significant differences: $*P < 0.05$, $**P < 0.01$, compared with control.

Aδ reflex and there was no depression of the C or Aδ radial nerve reflexes or any cardiovascular changes such as baroreflex sensitization [14]. This indicates first, that the drug had not spread rostrally in the CSF to affect the thoracic dorsal root area or the medulla; second, that the drug had not affected the renal sympathetic efferent pathway; third, that systemic absorption of the drug was insufficient to cause significant effect; and finally, therefore, that the effects of the drug were localized to the spinal cord.

A progressive increase in concentration to 5000 µg ml^{-1} in a total dose up to 7500 µg in a total volume of only 2 ml also abolished the tibial Aδ reflex (in addition to the C fibre reflex). The lack of effect on the radial Aδ reflex implies that the efferent sympathetic pathway remained unaffected, but the abolition of the radial C reflex and the reduction in both heart rate and arterial pressure, indicating baroreflex sensitization, suggests intrathecal spread, effective systemic absorption, or both. However, in view of the lack of effect of alfentanil 4.8 ml in the smaller concentration preparation on the radial C reflex, and in view of the maximum injected volume of only 2 ml in the large concentration, the more probable view is that the observed cardiovascular effects and the depression of the radial C reflexes were caused by systemic absorption.

It has been reported previously that, during systemic administration, the maximum depression of the cardiovascular system by fentanyl, alfentanil and sufentanil occurs at the point of maximum baroreflex sensitization, which also coincides with the abolition of somatic C fibre mediated reflexes [6–8]. Thereafter, further massive doses of these drugs causes no further cardiovascular depression [6–8, 15] although Aδ reflexes are abolished. The results of the present study suggest similar effects after i.t. administration.

This study also shows that alfentanil i.t. has a greater effect on C fibre mediated reflexes than on Aδ. The ratio of the concentration of alfentanil i.t. required for elimination of the Aδ and C fibres evoked responses was more than 10:1, which is similar to the ratio of the total dose of 11:1 for alfentanil administered systemically to produce comparable effects [7]. The precise mechanism for this selectivity of opioid on Aδ and C fibre reflexes is uncertain [16]. There is evidence that different opioid receptors may modulate the effects of different types of stimulation. For example the κ opioid agonists have a distinctly greater analgesic potency on tests of nociception using mechanical or visceral stimuli, in contrast with the µ agonists which have a greater effect on noxious heat stimuli [17–20]. At the cellular level, whereas µ and δ agonists act via potassium channels, the κ agonists act via calcium channels [16], which could possibly be one factor contributing to these observed differences.

An intriguing problem is the relationship between the lipophilicity and potency of the opioids administered i.t. McQuay and his associates have suggested an inverse relationship between lipophilicity and potency for a range of synthetic opioids injected i.t. in a rat model [21]. It has been shown that fentanyl administered i.t., in the same dog model as was used in the present study, abolished both Aδ and C reflexes at a total dose of only 128 µg [22]. This is in marked contrast with the results of the present study, showing that alfentanil, which is less lipophilic than fentanyl, was also less potent when administered i.t., particularly in relation to its effect on Aδ mediated reflexes, and hence would not support their hypothesis.

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SOMATOSENSORY AND AUDITORY EVOKED RESPONSES RECORDED SIMULTANEOUSLY: DIFFERENTIAL EFFECTS OF NITROUS OXIDE AND ISOFLURANE

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SUMMARY

Auditory (AER) and somatosensory evoked responses (SSER) were recorded simultaneously in eight patients under anaesthesia before surgery. We studied the effects of equi-MAC end-expiratory concentrations of isoflurane (0.65–0.75%) and nitrous oxide (60–65%). The anaesthetics were changed at random in three consecutive 10-min periods so that each patient received both drugs. From the AER recorded from the vertex and inion, Pa and Nb latency and amplitude were measured. N13, P20 latency and N13 amplitude were measured from SSER recordings from the neck and P15, N20, P25, N35, P45 latency and P15–N20, N20–P25, P25–N35 and N35–P45 amplitude from the scalp over the hand area of the sensory cortex. Compared with nitrous oxide, isoflurane significantly increased the latencies of the AER waves Pa ($P = 0.02$) and Nb ($P = 0.02$), and the SSER waves N20 ($P = 0.001$) and P25 ($P = 0.04$). We were unable to demonstrate significant differences in Pa and Nb amplitude between isoflurane and nitrous oxide that we had seen previously. However, the amplitude of the SSER wave N20 was reduced significantly by nitrous oxide compared with isoflurane ($P = 0.0004$). This wave (N20) is thought to emanate from the thalamo-cortical radiations, and our findings may be explained by an analgesic effect of nitrous oxide mediated by endogenous opioids.

KEY WORDS

Anaesthetics, gases: nitrous oxide. Anaesthetics, volatile: isoflurane. Brain: auditory evoked potentials, somatosensory evoked potentials.

The measurement of depth of anaesthesia is a challenge to anaesthetists. The anaesthetic state encompasses drug-induced loss of consciousness or hypnosis, analgesia, amnesia, lack of movement in response to surgical incision and prevention of changes in autonomic signs. This series of functional deficits is arranged conventionally in a descending hierarchy to correspond with a concept of deepening anaesthesia. The problem is that the components of the hierarchy are not necessarily interdependent, and they are not affected to the same degree at equal MAC values [1] by various anaesthetic techniques. If these various components could be assessed separately, then the development of an objective measure of depth of anaesthesia may be made easier. Separate assessment may also prove informative in the study of new anaesthetic drugs and may be useful in monitoring the additive or interactive effects of multiple drugs. Using evoked responses, we have attempted to separate the analgesic and hypnotic components of anaesthesia.

Isoflurane is thought to be a strong hypnotic, in contrast with nitrous oxide, which is recognized as a weak hypnotic drug, but a good analgesic. General anaesthetics increase the latency and depress the amplitudes of the evoked responses [2]. In a previous study, we compared the effects of isoflurane and nitrous oxide on the auditory evoked response [3]. We found that, at concentrations of nitrous oxide and isoflurane that were equipotent, using the MAC concept [1] isoflurane had a more depressant effect on the auditory evoked response than nitrous oxide [3]—the latencies were increased and the amplitudes reduced. An opposite finding has been reported by others [4] for the somatosensory evoked response. Nitrous oxide had a more potent effect on the cortical somatosensory evoked responses than approximately equipotent concentrations of isoflurane. The changes in the auditory evoked response may reflect predominantly the hypnotic component of anaesthesia, while those in the somatosensory response may reflect mainly the analgesic component. In order to investigate this further, and to counter any arguments concerning inter-laboratory differences in anaesthetic estimations, we have extended our previous study [2] and recorded the auditory and the somatosensory evoked responses simultaneously.

PATIENTS AND METHODS

We studied eight patients (five females) aged 26–47 yr and ASA I or II, who were undergoing major elective

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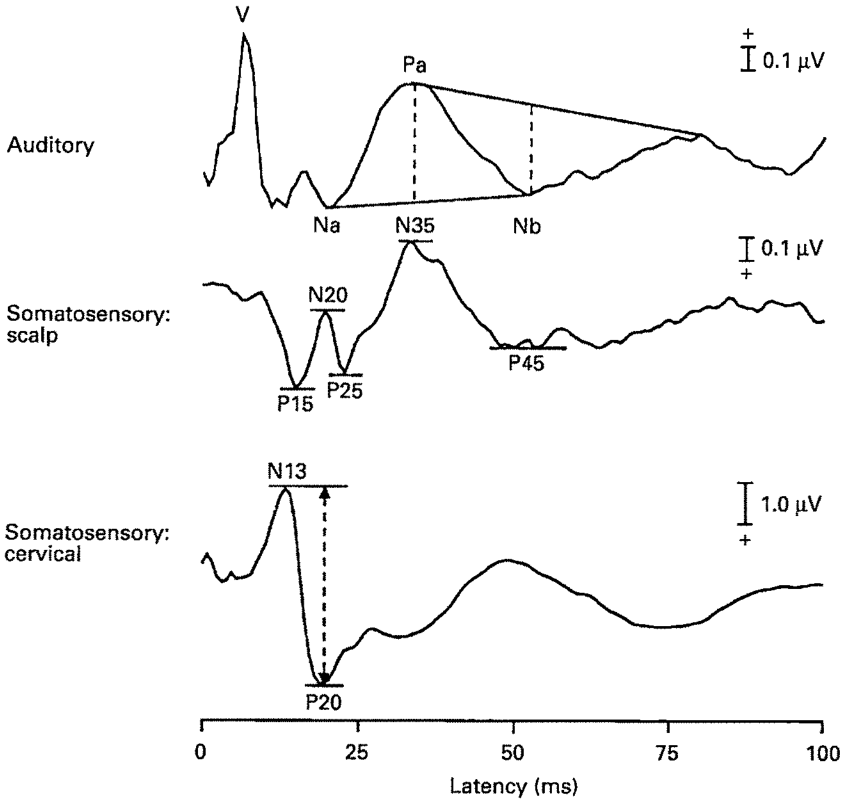

FIG. 1. Auditory (AER) and somatosensory (SSER) evoked responses to show latency and amplitude measurements. Latency was measured from time zero to the peak or trough in question. For the AER, the amplitude was taken as the height of the vertical from the peak (in the case of a positive wave, e.g. Pa) to where it bisects the line joining two neighbouring troughs. For example, the dotted lines on the top trace indicate Pa and Nb amplitude. For the SSER, the amplitude was taken as a vertical from a peak (in the case of a positive wave) to the succeeding trough. For example, the dotted line on the bottom trace indicates N13–P20 amplitude.

surgery. All gave informed consent to the study, which was approved by the Hospital Ethics Committee. Each patient was premedicated with papaveretum 0.25 mg kg^{-1} and hyoscine 5 μg kg^{-1} at least 1 h before induction of anaesthesia with thiopentone 2–4 mg kg^{-1}. Vecuronium 0.1 mg kg^{-1} was given i.v. and the trachea intubated. Mechanical ventilation of the lungs was adjusted to maintain an end-tidal $P\text{CO}_2$ of 4.0–5.5 kPa (Datex Capnomac). The inspired gas mixture was adjusted to produce the required end-expiratory concentrations: 60–65 % nitrous oxide or 0.65–0.75% isoflurane (Datex Capnomac); these concentrations were chosen to give approximately 0.6 MAC. The anaesthetic administered was changed randomly in each of the eight patients in three consecutive 10-min periods according to the treatment sequences recommended by Ebbutt [5]. The Capnomac analyser was calibrated using the manufacturer's calibration gas, and checked before and after each experiment using cylinders of isoflurane and Entonox, calibrated previously against volumetric standards using a gas chromatograph. Overpressure was used to reduce the time required to attain the target end-expiratory concentrations of isoflurane. Within 5 min, it was possible to have both stable end-expiratory values and residual concentrations of the previous agent less than 5 % of their original value.

Arterial pressure and heart rate were recorded every 2.5 min throughout the procedure using a Datascope automatic recorder. Nasopharyngeal temperature was recorded after tracheal intubation and at the end of the study period.

Recording the evoked responses

The auditory stimulus was a rarefaction click presented to both ears simultaneously at 75 dB greater than the average hearing threshold at a stimulus repetition rate of 6 s^{-1}. The somatosensory stimulus was a 150-μs electrical pulse produced by a constant current stimulator (Duostim) which had been modified by the addition of an optically isolated trigger input. This stimulus was applied to the median nerve at a rate of 2.2 s^{-1} and with sufficient current to produce a motor response. Both stimuli were applied continuously throughout the study.

Purpose-built amplifiers were used to record three channels of EEG onto FM tape. Electrode placements for the auditory evoked response (AER) were Cz-In, for the cervical somatosensory evoked response (SSER) Pz-C_{VII} and for the scalp SSER Pz-C3′ (20 mm back from C3 on the 10–20 system [6]). The gain was 100 dB for all channels. On replay, signals were analog filtered with bandwidths of 25–500 Hz for the AER and 10–500 Hz for the SSER. The evoked responses were analysed using a digital signal processing card resident in an IBM PC and purpose-designed software. This program provided automatic rejection of artefact and a range of digital filtering. For these data we used a high pass filter of 20 Hz and three-point smoothing.

The evoked responses were averaged over the last

2.8 min of each 10-min period when the end-expiratory concentrations were stable. Pa and Nb latency and amplitude were measured using our previous system (fig. 1). Latency was measured from time zero to the peak or trough in question. Amplitude was measured as the height of the vertical from the peak (in the case of a positive wave, e.g. Pa) to where it bisects the line joining two neighbouring troughs. This has the advantage of counterbalancing fluctuations in the baseline caused by low frequency waves on which the AER waves are sometimes superimposed. In contrast with the AER, the SSER is plotted with the negative deflection upwards. This is in order to comply with a long established convention. For the SSER, N13, P20 latency and N13 amplitude were measured from the cervical recordings and P15, N20, P25, N35, P45 latency and P15–N20, N20–P25, P25–N35 and N35–45 amplitude from the scalp recordings. The measurement convention shown in figure 1 was used to quantify the SSER and is that quoted most commonly in the literature.

Statistical methods

Analysis of variance was used to compare the effects of the agents and the periods during which the agents were administered on the AER and SSER variables, and to determine if there was an interaction between the effect of the drug and the period in which it was given. This study design improves the power of the test for interaction, as it is based on within-subject variability rather than the between subject variability used in the standard two-period crossover design.

RESULTS

Descriptive—AER

The AER of a patient during an isoflurane–nitrous oxide–isoflurane randomization sequence is shown in figure 2. Isoflurane depressed the amplitude of the early cortical waves Pa and Nb and increased their latencies, and when nitrous oxide was substituted this trend appeared to reverse. In this particular patient the amplitude and latencies in the second isoflurane period were not the same as those seen in the first isoflurane period. However, this effect was not statistically significant for the group as a whole.

Descriptive—SSER

Wave identification. The latencies of the waves of the individual SSER waveforms were measured. Average values (mean, SD) for the group of patients corresponded well with values reported previously. The prominent feature of the cervical SSER (fig. 1) was the negative wave N13 (14.5 (0.91) ms); Samra and colleagues [7] reported N13 as occurring at 14.8 ms at a similar anaesthetic concentration. This is followed by the positive wave which we have labelled P20 (20.4 (1.09) ms). The scalp SSER (figs 1, 3) was characterized by the positive wave which we have labelled P15 (16.3 (0.97) ms), followed by the negative N20 (20.6 (1.34) ms), and the positive P25 (25.7 (2.27) ms). McPherson and colleagues [4] have referred to these waves as the P1/N1/P2 complex and the latencies they reported were 15, 20 and 23 ms, respectively. Following these, we found the negative wave N35 (36.5 (2.98) ms) and a positive wave occurring at 56.0 (5.75) ms, which we assumed to be P45 lengthened by the anaesthetic. Sometimes an additional peak (fig. 3) occurred around 25 ms. This was disregarded in making measurements.

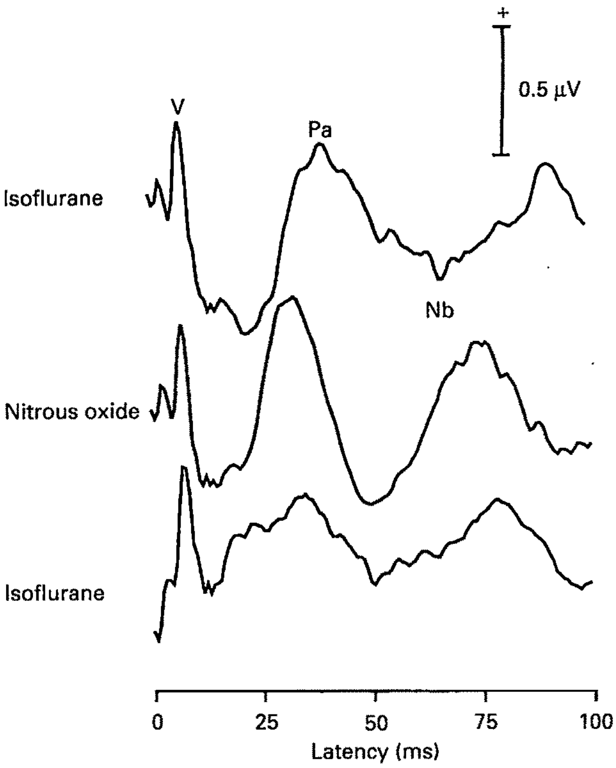

FIG. 2. Changes in the early cortical auditory evoked response of a patient who was given isoflurane, nitrous oxide and isoflurane for 10 min each. During the nitrous oxide period, Pa and Nb latencies decreased and their amplitudes increased compared with the isoflurane periods.

Measurement of the amplitudes and latencies of the various peaks in the individual patients yielded the following findings. In general, the cervical and scalp somatosensory latencies were increased with isoflurane compared with nitrous oxide. However, the latency of P15 of the scalp SSER was relatively invariable between agents such that it was used as an aid to identification: the scalp SSER of a subject during a nitrous oxide–isoflurane–nitrous oxide randomization is shown in figure 3. P15–N20 and N20–P25 amplitudes were greater and P25–N35 and N35–P50 amplitudes were less with isoflurane than with nitrous oxide.

Statistical analysis

There were no significant (5% level) effects or interactions related to period for either the AER or SSER. The differences between the effects of nitrous oxide and isoflurane on the early cortical auditory evoked response are shown in table I. The results for the latencies are similar to those of the previous study [3] also shown in the table. Isoflurane increased the latencies with respect to nitrous oxide (the difference is therefore negative). The trends in the amplitudes were in the same direction in both studies; however, in this study the differences

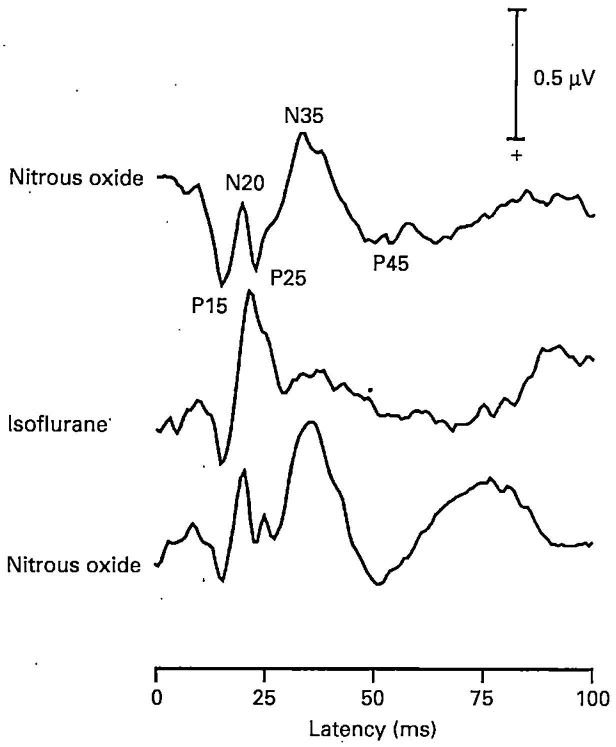

FIG. 3. Changes in the somatosensory evoked response recorded from scalp electrodes of a patient who was given nitrous oxide, isoflurane and nitrous oxide for 10 min each. During the isoflurane period, with the exception of P15 latency all the latencies increased compared with the nitrous oxide periods. Also P15–N20 and N20–P25 amplitudes increased and P25–N35 and N35–P45 reduced in the isoflurane period compared with the nitrous oxide period.

TABLE I. *Auditory evoked response latencies and amplitudes. Means for nitrous oxide (N_2O) and isoflurane (Iso.), differences between the means, standard error of the difference* (SED), *and significance of the difference. Values from the previous study* [3] *are show in parentheses*

	Means				
	N_2O	Iso.	Difference	SED	P
Latency (ms)					
Pa	35.0	40.7	−5.7 (−8.3)	2.4 (2.5)	0.02 (0.01)
Nb	52.6	62.5	−9.9 (−8.1)	4.0 (4.0)	0.02 (0.08)
Amplitude (µV)					
Pa	0.55	0.37	0.18 (0.54)	0.12 (0.11)	0.16 (< 0.001)
Nb	0.43	0.41	0.02 (0.38)	0.09 (0.10)	0.8 (0.004)

TABLE II. *Somatosensory evoked response latencies. Means for nitrous oxide (N_2O) and isoflurane (Iso.), differences between the means, standard error of the difference* (SED), *and significance of the difference*

	Means				
	N_2O	Iso.	Difference	SED	P
Cervically recorded					
N13	14.4	14.6	−0.2	0.1	0.07
P20	20.2	20.8	−0.6	0.3	0.06
Scalp recorded					
P15	16.4	16.4	0	0.1	1.0
N20	20.2	21.2	−1.0	0.2	0.001
P25	24.8	26.7	−1.9	0.8	0.04
N35	35.9	37.3	−1.4	0.7	0.09
P45	54.1	58.0	−3.9	2.4	0.16

TABLE III. *Somatosensory evoked response amplitude. Means for nitrous oxide (N_2O) and isoflurane (Iso.), differences between the means, standard error of the difference* (SED) *and significance of the difference*

	Means				
	N_2O	Iso.	Difference	SED	P
Cervically recorded					
N13–P20	3.6	3.9	−0.3	0.2	0.3
Scalp recorded					
P15–N20	0.28	0.55	−0.28	0.06	0.0004
N20–P25	0.64	0.84	−0.20	0.10	0.07
P25–N35	1.26	0.99	0.27	0.13	0.08
N35–P45	1.20	0.95	0.25	0.22	0.3

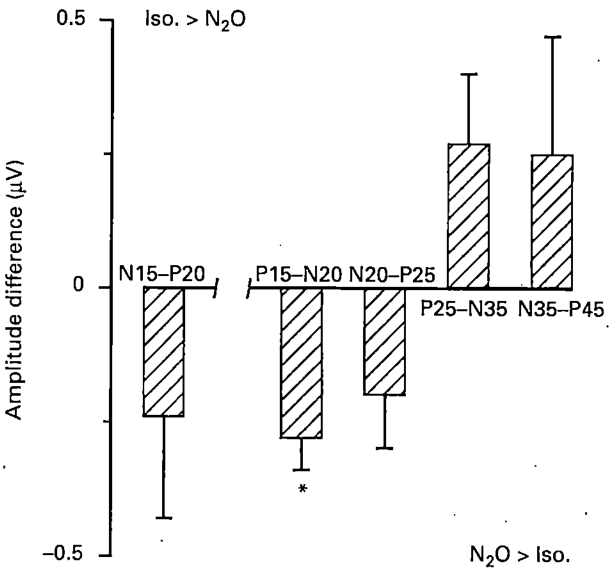

FIG. 4. The difference and standard error of the difference in the effects of nitrous oxide (N_2O) and isoflurane (Iso.) on the somatosensory evoked response recorded from the neck and scalp. Positive values indicate that the attenuating effect of isoflurane is greater than that of nitrous oxide. * $P = 0.0004$.

between the two drugs were much smaller and not significantly different from zero.

The differences between the effects of nitrous oxide and isoflurane on the SSER latencies are shown in table II. Significant differences occurred in N20 and P25.

The differences between the effects of nitrous oxide and isoflurane on the SSER amplitudes are shown in table III and plotted in figure 4. The amplitudes in the early section of the response (N13–P20, P15–N20 and N20–P25) were greater with isoflurane than with nitrous oxide and in the later section (P25–N35 and N35–P45) were greater with nitrous oxide than with isoflurane. A significant difference occurred in P15–N20.

Other physiological variables

Systolic arterial pressure and heart rate were significantly greater in the first 10-min period, which included tracheal intubation, compared with the second and third periods (systolic pressure difference 5.8 (SED 1.1) mm Hg) ($P = 0.0002$); heart rate difference 18.4 (2.6) beat min^{-1} ($P = 0.0001$), as would be expected. Systolic arterial pressure was slightly but significantly less (4.6 (1.1) mm Hg) with administration of isoflurane compared with nitrous oxide ($P < 0.001$). In all patients, temperatures remained within the range 35.5–36.7 °C during the period of investigation and there were no effects that could be attributed to differences between the periods or drugs. The patients appeared to be anaesthetized adequately during the study, and no patient volunteered recall of any event during anaesthesia.

DISCUSSION

The hypothesis tested in the study was that the early cortical auditory evoked response represented by waves Pa and Nb reflects the hypnotic component of anaesthesia and would be expected to be affected more by isoflurane than by nitrous oxide. In contrast, the somatosensory evoked response, in particular wave N20, reflects the analgesic component of anaesthesia, and would be affected more by nitrous oxide than by isoflurane. In constructing this hypothesis, isoflurane was assumed to be a potent hypnotic and weak analgesic and nitrous oxide a weak hypnotic and potent analgesic. This requires qualification.

First, we need to define "hypnosis" and "analgesia". Prys-Roberts [8], in an attempt to define these terms, started with the premise that *pain* is the conscious perception of a noxious stimulus. He defined *anaesthesia* as that state in which, as a result of a drug-induced unconsciousness, the patient neither perceives nor recalls noxious stimulation. *Hypnosis* was conceived as synonymous with anaesthesia, as it implies a drug-induced sleep and *analgesia* as diminished or abolished perception of pain in an otherwise conscious patient. However, we feel that the concept of analgesia may be extended to the anaesthetized patient. For example, analgesic drugs such as fentanyl and morphine reduce the amount of inhalation agent required to anaesthetize a patient. Using the concept of MAC (minimum alveolar concentration which prevents movement in response to surgical incision in 50 % of patients) as a measure of anaesthetic potency [1], morphine reduces MAC for the inhalation agents by up to 75 %. However, neither fentanyl nor morphine alone produces anaesthesia. It is clear from this that there are at least two (there may be more) components of anaesthesia, an analgesic one provided by drugs such as fentanyl and morphine and an hypnotic one, which "puts the patient to sleep".

This study supports our hypothesis that there are aspects of the SSER which reflect analgesia rather than hypnosis, in that we have demonstrated a greater reduction in amplitude of P15–N20 with nitrous oxide compared with isoflurane. This is in contrast with our findings in the AER, where there was no significant difference between the effects of each anaesthetic on Pa and Nb amplitude. In the present study, there were differences in the AER results compared with our previous study, but these did not affect our conclusions. In this study, the changes in the early cortical waves Pa and Nb were not affected by period. In our previous study Pa and Nb had shown greater amplitudes and shorter latencies in the first period compared with the second and third. Also, the reduction in Pa and Nb amplitudes by isoflurane compared with nitrous oxide were not significant in this study, whereas previously they were. One possible explanation for this is that the simultaneous somatosensory stimulation may have lightened the depth of anaesthesia under isoflurane, and hence decreased the difference in effect between the two agents. Clearly, it is necessary to study more subjects in order to resolve this discrepancy.

The studies most comparable to ours on the relative effects of isoflurane and nitrous oxide on the median nerve somatosensory evoked response are those of McPherson and colleagues [4], Restuccia and colleagues [9] and Peterson, Drummond and Todd [10]. McPherson's group found, as we have, that isoflurane increased N20 latency more than nitrous oxide, and that nitrous oxide reduced N20 (N20–P25 in our study) amplitude more than isoflurane. The isoflurane concentrations in their study were 0.25–1.0 % (0.22–0.87 MAC) and this was compared with 60 % nitrous oxide (0.48 MAC). Restuccia and colleagues [9] found that N20 latency was greater and the amplitude (P15–N20) was depressed less with 1.0 MAC isoflurane on its own than with 0.5 MAC isoflurane and 67 % nitrous oxide in oxygen (total of 1.14 MAC). Our study supports these findings. Peterson, Drummond and Todd came to different conclusions. They found that N20 latency was greater, but that the amplitude (N20–P25) was depressed more by 1.5 MAC isoflurane on its own than by a 1.58 MAC mixture of isoflurane and nitrous oxide. At 1.5 MAC isoflurane, N20 could be detected in only four of the seven patients, compared with seven of seven when they were receiving the 1.58 MAC mixture. The suggestion here is that 0.5 MAC isoflurane reduced the amplitude of N20 (N20–P25) more than 0.58 MAC nitrous oxide.

Other studies report practically no effect of nitrous oxide on N20 latency [11, 12], whereas a definite and substantial increase has been reported with isoflurane [7, 13]. Both nitrous oxide and isoflurane are reported to reduce the amplitude of N20 [7, 11–13], but precisely which agent has the greater effect cannot be determined from these studies.

In addition to comparing the relative effects of nitrous oxide and isoflurane on the AER and SSER, this investigation allowed us to compare relative effects of anaesthetics in different sections of the somatosensory neuraxis. Others have found that the earlier waves were relatively robust to the effects of anaesthetics [7, 9, 12]. Not surprisingly, therefore, we found no significant differences between the two drugs in the effects on the cervically recorded waves and the scalp recorded wave P15. These waves are thought to be generated at the level of, or caudal to the medial lemniscus [14]. Nitrous oxide therefore, does not appear to antagonize nociceptive transmission at that level.

N20 wave latency was the earliest to show a statistically significant difference. The subsequent wave P25 also showed a statistically significant difference. In all cases where there was a change, the latencies were longer with isoflurane than nitrous oxide. It would seem, therefore, that isoflurane slows transmission more than nitrous oxide from around 13–20 ms onwards and, because more synapses have to be crossed to reach to the higher regions of the tract, the waves originating from higher centres are more affected than those generated more caudally. Also, it appears that changes in wave latency reflect hypnosis rather than analgesia.

N20 amplitude, when measured from the preceding peak, P15, showed a statistically significant difference; when measured to the succeeding wave, P25, which is the amplitude measurement reported most often in the literature, the difference between the two drugs approached significance ($P = 0.07$). In both these cases, nitrous oxide reduced the amplitude compared with isoflurane. In contrast, after 25 ms the amplitudes of P25–N35 and N35–P45 were greater for nitrous oxide than for isoflurane, but these differences were not statistically significant, although for P25–N35 amplitude it was close ($P = 0.08$).

N20 and P25 originate from the region of the thalamus and primary cortex [14–16]. The amplitude of N20 (latency span of 15–25 ms) was depressed more by nitrous oxide than by isoflurane and we speculate that, between the medial lemniscus and primary somatosensory cortex, there are structures involved in analgesia. Rostral to the primary somatosensory cortex are the frontal cortex and association areas, represented by waves N35 and P45. These structures may be involved more in hypnosis, in that the amplitudes measured in this study were similar and both agents were probably exerting a similar depressive effect. Two sources of information support these ideas. Freye, Buhl and Ciaramelli [17] found that N20 decreases in a dose-related way with alfentanil, an opioid binding to the μ receptor. This can be antagonized by increasing the stimulus amplitude or by administering naloxone. Alfentanil had no effect on a later N100 wave which they investigated. The likely generators of this wave, which we did not study, are also in the frontal cortex and association areas. In contrast, nalbuphine, an opioid with κ agonist activity, did not affect N20, but reduced the amplitudes of N100. This was antagonized by increasing the stimulus amplitude, but not by naloxone. The authors suggested that, as N20 is primarily generated in the pontine–thalamic region, the mode of action of fentanyl resembles that of the block of sensory impulses. This takes place before impulses are transmitted to more rostral structures responsible for the identification of pain. The effect of nalbuphine on late evoked potentials may indicate an activity on the thalamo–cortical projection sites which are involved in perception of pain. This could be the mechanism for an analgesic effect attributed, to a greater or lesser extent, to all volatile anaesthetic agents when they are used in small concentrations for obstetric analgesia [18–20]. Nitrous oxide may, therefore, exert its analgesic effect in two ways. First, it may stimulate the production of endogenous opioids which act at receptors in the pain pathways. (This would explain the strong attenuation of N20 emanating from the thalamus.) The evidence for this mechanism has been reviewed extensively by Finck [21] and rests on the antagonism of the analgesic effects by naloxone, and the development of tolerance. Second, nitrous oxide may act directly on the cortex to diminish pain perception, which accords with our own findings [22] and those of others [23, 24] that nitrous oxide depresses that part of the auditory evoked response thought to be generated by the primary and frontal cortex and association areas.

In conclusion, we have demonstrated a clear difference in the effect of nitrous oxide on the N20 wave of the SSER when compared with isoflurane. This contrasts with cortically derived waves of both the AER and the SSER, on which the effects of the two drugs were similar. These changes in the evoked responses could provide a basis for further research into the effects of both hypnotic and analgesic drugs used in anaesthesia.

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VOLTAGE FIELDS SURROUNDING NEEDLES USED IN REGIONAL ANAESTHESIA

R. P. JONES, M. DE JONGE AND B. E. SMITH

SUMMARY

Using a bench model, we have studied the voltage fields surrounding both insulated and uninsulated needles used in regional anaesthesia. The findings were compared with earlier computer predictions which suggested that the fields would be markedly different for the two types of needle. The results confirm that the fields differ markedly and suggest that the use of insulated needles may not necessarily improve the accuracy of nerve location and that uninsulated needles may be more appropriate.

KEY WORDS

Anaesthetic techniques: regional anaesthesia. Equipment: insulated needles, peripheral nerve stimulator. Physics: voltage fields.

Low power peripheral nerve stimulators are now used frequently to aid nerve location during regional anaesthesia [1], but there is still controversy regarding the need for insulation of the needles, particularly with regard to the nature of the voltage field which surrounds the different types of needle. Several workers have attempted to quantify these fields. Montgomery and colleagues [2] used conductive paper to measure the voltage field strength at various points around the shaft and tip of uninsulated needles and concluded that maximum current density occurred at the tip of the needle. This study may be criticized on the lack of experimental detail and on the non-biological nature of the model, particularly as regards the electrical resistance of the paper, which was probably several orders of magnitude greater than that found in human tissues. A computer simulation by Bashein, Haschke and Ready [3] suggested that the voltage fields for insulated and uninsulated needles differed markedly. This model might also be criticized on the grounds that it is non-biological and may have used unrealistic boundary conditions to derive the solutions to the Laplace equations upon which the simulation was based.

The present study was undertaken to determine the form and magnitude of the voltage field surrounding different needles in a physiologically compatible model, and to compare the observed results with the earlier computer simulation.

MATERIALS AND METHODS

A rectangular Perspex tray of dimensions 30 cm × 20 cm × 3 cm was filled to a depth of 5 mm with 4.5% human albumin solution (HAS). A 22-gauge Pole needle (Top, RDG Electro-medical) was used as the insulated test needle and a 22-gauge Whitacre pointed spinal needle (Monoject) as the uninsulated needle.

The needle under test was inserted through the centre of one short side of the tray to project 3 cm into the solution (fig. 1). The earth electrode was positioned at the opposite end of the tray. The whole tray was positioned over a sheet of 1-mm grid graph paper to permit accurate measurement of the position of the test and probing needles. A potential difference of 3.0 V was maintained between the test needle and the earth electrode, the needle being negative with respect to the earth, by a constant voltage source (Koutant LA 100.2).

Voltage measurements were made using an electronic voltmeter with an input impedance in excess of 10 MΩ (Maplin Gold, Maplin Ltd), and an uninsulated seeking electrode of the same material as the needle under test. This needle was inserted vertically to the full depth of the tray to ensure that the maximum voltage at each point was recorded in a consistent manner and so that the model was effectively two-dimensional.

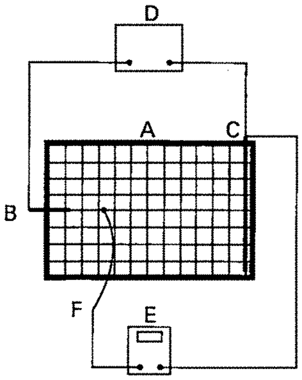

FIG. 1. The bench model. A = Tray containing human albumin solution; B = test needle; C = earth electrode; D = constant voltage source; E = voltmeter; F = probe needle.

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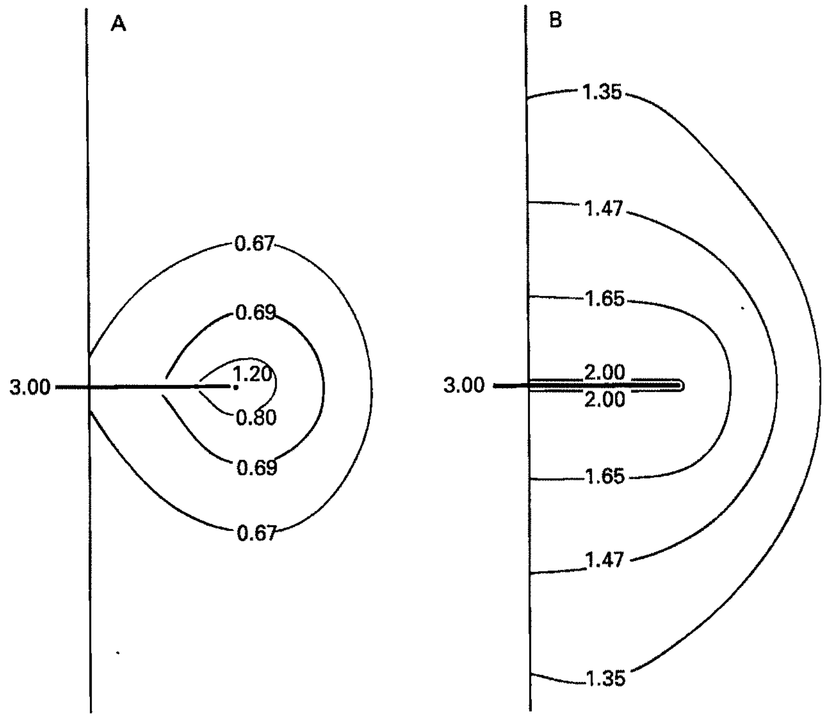

FIG. 2. Isopotential lines surrounding the insulated needle (A) and the uninsulated needle (B).

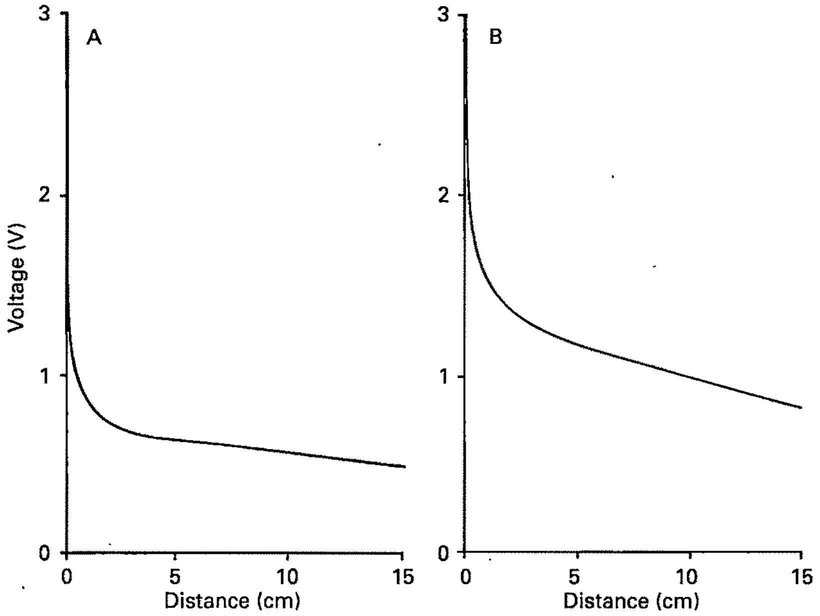

FIG. 3. Voltage plot as a function of distance from the needle tip in the direction of the needle. A: Insulated needle; B: uninsulated needle.

Two sets of voltage readings were made. In the first, the voltage was measured at fixed points between the tip of the test needle and the earth plate. In the second, the probe needle was positioned to identify points of equal voltage surrounding the needle tip—the isopotential points.

RESULTS

The results for both needle types are presented in figures 2 and 3. Figure 2A shows the isopotential lines surrounding the insulated needle, while figure 2B shows the field for an uninsulated needle. The isopotential lines show that there was an approximately circular voltage field surrounding the insulated needle, while that for the uninsulated needle was markedly non-uniform.

Figure 3 shows the fixed point voltage measurements for both insulated and uninsulated needles. For the insulated needle (fig. 3A), at any given distance from the needle tip the measured voltage was less than the corresponding point for the uninsulated needle (fig. 3B). In addition, the gradient of the slope was greater for the uninsulated needle than for the insulated.

The relationship of voltage gradient to distance from the needle tip, over the first 1 cm from the tip, is shown for both needles in figure 4. Curve a is the

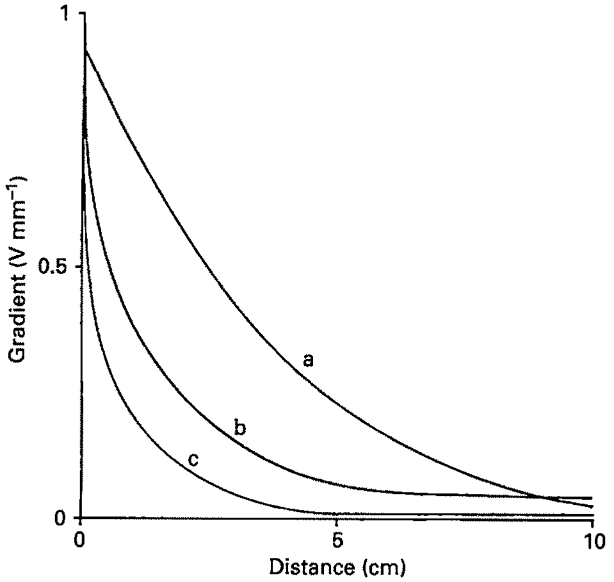

FIG. 4. Voltage gradient as a function of distance from the needle tip. a = Gradient in front and to the side of an insulated needle; b = gradient to the side of an uninsulated needle; c = gradient in front of an uninsulated needle.

voltage gradient for the insulated needle, which was the same to the side as in front of the needle tip. Curve b is the gradient found to the side of the tip of the uninsulated needle. Curve c represents the gradient in the region immediately in front of the tip of an uninsulated needle. At a point approximately 2–3 mm from the needle tip, the voltage gradient for the insulated needle was two to three times greater than at the side of an uninsulated needle, and six times greater than in front of the tip of the uninsulated needle.

DISCUSSION

The voltage across a resting nerve cell membrane is approximately 80 mV, the inside of the nerve being negative with respect to the surrounding medium [4]. If sufficient movement of ions can be produced by the application of a voltage gradient, then the transmembrane potential may be reduced to 55 mV. At this point the membrane becomes freely permeable and a spike potential is generated. The movement of ions occurs in proportion to the magnitude of this voltage gradient. The form and magnitude of the voltage field surrounding the needle used for nerve block is therefore important.

Using an electronic, high-impedence voltmeter it is possible to measure directly the voltage field surrounding a needle. The impedance of the voltmeter is crucial to accurate measurement. If the impedance is low, the meter draws significant current from the model, in essence short-circuiting the voltage field, with consequent distortion of the shape of the field. The problem diminishes as the impedance of the voltmeter increases. For a needle voltage of 3.0 V, the current in the model was 0.9 mA using an insulated needle and 8.6 mA using an uninsulated needle. Therefore the resistance of the model was 3333 Ω and 349 Ω, respectively. (The difference in resistance of the total circuit results from the surface area of the needle in contact with the HAS being smaller in the case of the insulated needle.) Using a high impedance voltmeter of 10 MΩ, the measuring circuit would draw 0.0333 % and 0.0035 % of the total current of the model, respectively.

The two-dimensional nature of the study by Montgomery and colleagues [2] has been criticized. This criticism is unjustified, as the prediction of a three-dimensional field from a two-dimensional analysis is standard practice in the study of voltage fields [5]. Our model was effectively two-dimensional, but the real fields may be assumed to be the three dimensional "solid of revolution" of the isopotential plots, except that the potential gradients are steeper close to the needle. In two dimensions, the circumference of isopotential lines (if they are circular) increases in proportion to the radius. When working in three dimensions, the areas of the isopotential surfaces (if they are spherical) increase in proportion to the radius squared. Therefore current density, and hence potential gradient, declines more rapidly with distance in a three-dimensional model. Although a similar argument applies to the non-circular lines or non-spherical surfaces of the uninsulated needles, the mathematical relationship is less clear.

Montgomery's study was criticized also on the basis that the resistance of conductive paper is usually much greater than that of normal tissues, but as no details of their method were given, it is not possible to comment further. For this study, we chose 4.5 % HAS to simulate more closely the clinical situation.

The isopotential lines may be regarded in the same way as contour lines on a map or isobars on a weather map. The maximum voltage gradient is found where the isopotential lines are most dense. From figure 2A it is clear that there is an almost circular voltage field surrounding the tip of an insulated needle, whereas with the uninsulated needle the lines are most dense in front of the needle (fig. 2B). This supports the theoretical analysis of Bashein, Haschke and Ready [3]. As the nerve is most likely to be stimulated when it lies within a steep voltage gradient, with an uninsulated needle the nerve is most likely to fire when it lies immediately in front of the needle tip. With the insulated needle, the nerve is just as likely to fire when it is adjacent to the needle tip as when it lies in front of it. The nerve would also be stimulated just as readily when it lies behind the needle tip as would occur if the nerve had been transfixed by the needle. The voltage gradient found in front of the uninsulated needle tip (curve c in figure 4) would result in stimulation only when the needle was within approximately 2 mm of the nerve. From figure 4 curve a, it follows that a nerve lying several millimetre to the side of an insulated needle could be fired by the greater voltage gradient found here than would be the case with the uninsulated needle. Such a situation may have occurred in the study by Ford, Pither and Raj [6], who compared insulated and uninsulated needles for sciatic nerve location in the cat, using pulse-synchronous muscle twitch to aid nerve location. With the uninsulated needle it was clear that, in the five animals studied, the needle had come within 1 mm of the sciatic nerve in each case, while for the insulated needle three of seven had completely missed the nerve, but had stimulated the nerve. These three cases were excluded from further analysis. Because of this exclusion, while all the cases performed with uninsulated needles were studied, only the best of the insulated needles were included. The principal finding of the study, that insulated needles appeared to result in greater accuracy of nerve location, may be flawed. If the three excluded cases are included in the analysis, the uninsulated needle appears to give the most accurate location of the nerve.

Figure 3A shows that the voltage in front of an insulated needle decreased rapidly over the first 1 cm and then declined only slowly over the next few centimetre. With the uninsulated needle (fig. 3B), the initial voltage decrease was steep, but less than that with the insulated needle, while the decline in voltage over the next few centimetre was noticeably steeper. Assuming that, in clinical practice, the nerve should lie 1–2 mm in front of the tip of the blocking needle, the injection of local anaesthetic solution would displace the nerve from the needle. This would effectively move the nerve down the slope of the voltage gradient, sharply reducing the response of the nerve to stimulation and producing the "fade" effect seen in practice after injection of local anaesthetic solution [7]. The fade is greatest (and may only be seen) if the movement of the nerve is within the steepest part of the curve—that is, the first 5 mm. Fade therefore may be used as a guide for proximity of needle tip to nerve with both needles.

While it might appear to be logical to use insulated needles in regional anaesthesia for greater accuracy of nerve location, this conclusion cannot be supported. From the data presented, it would appear that it is necessary to re-examine the role of the less expensive and more widely available uninsulated needle in electrical nerve stimulation in regional anaesthesia.

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ARTERIAL OXYGEN SATURATION DURING INDUCTION OF ANAESTHESIA AND LARYNGEAL MASK INSERTION: PROSPECTIVE EVALUATION OF FOUR TECHNIQUES

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SUMMARY

In a prospective, randomized study of 87 patients, we have compared the incidence of hypoxaemia during induction of anaesthesia with subsequent Laryngeal Mask Airway (LMA) insertion in healthy adults when four different techniques were used: one without supplementary oxygen, and three with supplementary oxygen. Twelve patients did not receive supplementary oxygen before LMA placement, 25 underwent partial denitrogenation by breathing oxygen from the start of injection of the induction agent, 25 underwent formal denitrogenation by breathing oxygen for 3 min, and 25 received five tidal volume breaths of oxygen by face mask using positive pressure immediately after induction of anaesthesia. Anaesthesia was induced with propofol 2.0 mg kg^{-1} and fentanyl 1 μg kg^{-1}. Additional propofol was given if required. Arterial oxygen saturation was measured by pulse oximetry. Desaturation occurred in 11 of 12 patients who did not receive supplementary oxygen, and in 19 of 25 patients who received manual ventilation with 100% oxygen after induction of anaesthesia before LMA insertion. Full denitrogenation and partial denitrogenation were equally successful in preventing desaturation. Failure to position the LMA successfully occurred in 3% of patients, and some difficulty was encountered in another 18%.

KEY WORDS
Anaesthetic techniques: induction. Complications: hypoxaemia. Equipment: laryngeal mask airway. Oxygen: supplementation.

Arterial oxygen saturations of 90% or less have been reported to occur with a frequency of 25% during induction of anaesthesia in unselected patients [1]. Previous studies have illustrated the benefit of partial denitrogenation, and cast doubt on the efficacy of positive pressure ventilation with a face mask after induction of anaesthesia with thiopentone [2].

Induction of anaesthesia with propofol may result in a period of apnoea [3, 4] during which hypoxaemia may occur. As propofol is now used widely and the LMA is used commonly for airway maintenance, we have studied the incidence of hypoxaemia which occurred when anaesthesia was induced with propofol and fentanyl and an LMA inserted. We evaluated four techniques: in one group, patients breathed room air before and during induction of anaesthesia, and in the three other groups different techniques of supplementary oxygenation were used.

PATIENTS AND METHODS

In a prospective, randomized design, we studied 87 healthy (ASA I or II) patients aged 17–65 yr undergoing elective surgery for which use of the LMA was considered appropriate, including minor gynaecological and general surgical procedures. Hospital Ethics Committee approval was granted, and informed patient consent obtained. Patients were not studied if there was evidence of cardiac or respiratory disease, obesity or a history of gastro-oesophageal reflux.

On admission to the anaesthetic room, each patient was allocated randomly to one of four groups by selecting from unmarked, sealed envelopes. Patients in group A breathed room air before insertion of the LMA. Patients in group B were asked to breathe normally from an anaesthetic face mask applied from the start of propofol injection until loss of consciousness. During this period, oxygen was supplied at 8 litre min^{-1} via a Mapleson A breathing system. No attempt was made to guarantee an airtight seal, and patients themselves were asked to hold the mask in position. Patients in group C underwent formal denitrogenation for 3 min, ensuring an airtight seal, via a Mapleson A breathing system with an oxygen flow of 8 litre min^{-1} before injection of propofol. Those in group D did not undergo denitrogenation, but after loss of consciousness, an oropharyngeal airway was inserted and five positive pressure breaths of simulated tidal volume were applied by the anaesthetist using a face mask and an oxygen flow of 8 litre min^{-1} via a Mapleson A breathing system before insertion of the LMA.

All patients received premedication with temazepam 20 mg approximately 1 h before anaesthesia. Anaesthesia was induced with fentanyl 1 μg kg^{-1}, and propofol 2 mg/kg body weight injected over 20 s via a 20-gauge cannula in the dorsum of the hand. Additional increments of propofol were given

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TABLE I. *Patient characteristics (mean* (SD) *[range]) and oxygenation on admission to the anaesthetic room (median [range] (Q1–Q3)). Between-group comparisons:* $P = 0.387$ *for age,* $P = 0.837$ *for weight (ANOVA);* $P > 0.05$ *for* Sp_{O_2} *on admission (Kruskal–Wallis statistic = 5.1 corrected for ties)*

	Group A ($n = 12$)	Group B ($n = 25$)	Group C ($n = 25$)	Group D ($n = 25$)
Age (yr)	41.2 [22–65]	39.2 [24–57]	36.2 [17–62]	34.7 [19–58]
Weight (kg)	64.4 (11.7) [40–82]	65.6 (11.7) [50–100]	65.8 (11.2) [50–85]	67.7 (10.4) [50–86]
Sex (M/F)	1/11	3/22	4/21	6/19
Sp_{O_2} on admission to anaesthetic room (%)	97.1 [96–98] (97.0–97.8)	97.6 [96–99] (97.0–98.0)	97.3 [96–99] (97.0–98.0)	97.1 [96–98] (97.0–98.0)

TABLE II. *Smallest* Sp_{O_2} *values from beginning of propofol injection until 60 s after satisfactory airway confirmed. Kruskal–Wallis test corrected for ties:* $KW = 52.16$*;* $P < 0.001$*. Multiple inter-group comparisons using the Mann–Whitney U test reveal: group A differs from groups B or C, but not from group D; group D differs from groups B or C (*$P < 0.0001$ *for these comparisons); groups B and C do not differ*

	Group A ($n = 12$)	Group B ($n = 25$)	Group C ($n = 25$)	Group D ($n = 25$)
Median (%)	89.5	98.0	98.0	93.0
Inter-quartile (%)	81.8–92.8	98.0–99.0	97.5–99.0	88.0–96.0
Range (%)	71–98	95–100	95–100	73–99
95% confidence interval (%)	81.8–92.7	98.0–99.0	98.0–99.0	88.2–95.8

as necessary. When an adequate depth of anaesthesia was attained, an LMA was inserted as described by Brain [5]. All the anaesthetics were given by the authors, who were experienced in the use of the LMA. A size 3 LMA was used for women, and a size 4 for men.

Each patient was monitored with a pulse oximeter (Datex Satlite or Critikon Oxyshuttle). Patients were excluded from the study if the arterial oxygen saturation (Sp_{O_2}) was less than 96% with the subject in a supine position breathing room air. The following observations were recorded by an independent observer: Sp_{O_2} on admission to the anaesthetic room; least Sp_{O_2} occurring from the start of propofol injection until 60 s after confirmation of satisfactory LMA placement; time taken from commencement of propofol injection until either confirmation of satisfactory LMA placement or establishment of ventilation by an alternative technique. Satisfactory LMA placement was confirmed when the patient's lungs could be inflated easily by gentle positive pressure. The pulse oximeter display was not visible to the anaesthetist, and the audible tone was silenced. If the Sp_{O_2} decreased to 85%, the anaesthetist was informed by the observer and oxygenation was restored as rapidly as possible, with or without the use of the LMA as appropriate.

Ease of LMA placement was assessed as: 1 = success at the first attempt; 2 = successful, but with some difficulty for any reason, including inadequate depth of anaesthesia necessitating propofol increments; 3 = attempts at LMA insertion abandoned.

Concern regarding low Sp_{O_2} values in group A prompted preliminary inspection of results. This showed that in 11 of the 12 patients in this group there was a reduction in Sp_{O_2}, and in six patients there was a reduction to less than 90% during LMA insertion. This limb of the study was therefore abandoned.

Results were analysed by analysis of variance for parametric data, and by Kruskal–Wallis, Mann–Whitney, or chi-square tests for non-parametric data. Where possible, statistical calculations were carried out using the Minitab 7.2 statistical software package on an Olivetti PCS 286 personal computer with the MS DOS 3.3 disk operating system.

RESULTS

Eighty-seven patients were studied: 12 in group A, and 25 in each of the three other groups (table I). There were no significant differences in age, weight or Sp_{O_2} on admission. There were similar numbers of men and women in each group.

A decrease in Sp_{O_2} to less than pre-induction values occurred in 11 of the 12 patients in group A, and in 19 of the 25 patients in group D. Only two patients in group B and two patients in group C experienced a decrease in Sp_{O_2}. The smallest Sp_{O_2} values recorded from the start of propofol injection until 60 s after either confirmation of satisfactory LMA insertion or establishment of ventilation by alternative techniques in the patients in whom LMA placement was unsuccessful are presented in table II.

There was no significant difference between the results in groups A and D. In both these groups the median Sp_{O_2} decreased significantly. There was no decrease in the median Sp_{O_2} in either group B or group C. There was no correlation between body weight and any decrease in Sp_{O_2} among the subjects in groups A and D (Pearson correlation coefficients between weight and Sp_{O_2}: -0.048 for group A, 0.035 for group D).

Full denitrogenation and partial denitrogenation were equally successful in preventing desaturation.

The ease of LMA insertion is summarized in table III. There was no significant inter-group difference in the numbers of patients in whom LMA placement was unsuccessful at the initial attempt ($\chi^2 = 1.175$; $P > 0.1$). The LMA was not inserted satisfactorily in three patients; in one because of difficulty in adequately deepening anaesthesia, and in two because of anatomical factors. In all three cases of failed insertion, alternative techniques of airway management were used without difficulty.

TABLE III. *Ease of insertion of laryngeal mask airway.* $\chi^2 = 1.175$, $P > 0.1$—*first attempt compared with difficulty/failed*

	Group A ($n = 12$)	Group B ($n = 25$)	Group C ($n = 25$)	Group D ($n = 25$)	Total ($n = 87$)
At first attempt	9	21	20	18	68 (78 %)
With difficulty	2	3	4	7	16 (18 %)
Failed	1	1	1	0	3 (3 %)

TABLE IV. *Time (mean* (SD) *[range]) from start of induction to confirmation of satisfactory LMA placement (excluding failed placements). Group D differs from groups A, B and C when compared either individually or collectively using Student's t test* ($P < 0.01$) *and using analysis of variance* ($P = 0.004$)

	Group A ($n = 11$)	Group B ($n = 24$)	Group C ($n = 24$)	Group D ($n = 25$)
Time (s)	58.6 (23.7) [25–96]	52.7 (14.6) [30–80]	56.9 (33.9) [25–80]	80.3 (31.3) [37–180]

There were no significant differences in times from the initiation of propofol injection until confirmation of a satisfactory airway using the LMA between groups A, B or C (table IV). However, this was significantly longer in group D, compared with the three other groups either collectively or individually ($P = 0.004$; repeated analysis of variance).

DISCUSSION

We have found a 3 % failure rate of insertion of an LMA and, in 18 % of patients, insertion was accomplished only after varying degrees of difficulty. This is comparable to the findings of other authors: Brodrick, Webster and Nunn [6] reported a 2 % failure rate and an 18 % incidence of difficulty, whilst Maltby, Loken and Watson [7] reported a 4.8 % failure rate and 20.4 % rate of difficulty.

Our incidence of 18 % difficulty includes patients in whom there was inadequate depth of anaesthesia initially and it was usually easy to insert an LMA placement when more propofol had been given.

The following factors may contribute to the high incidence of desaturation in patients in groups A and D: the respiratory depressant effect of propofol [3, 4]; airway obstruction between administration of propofol and insertion of the LMA; modest oxygen reserves (approximately 450 ml) when patients breathe air at functional residual capacity [8].

The mean time from the start of induction of anaesthesia to establishing an airway using the LMA in patients in group A was 67.7 s, and the median values for the least Sp_{O_2} during this period was 89.5 %. These results are in accord with previous work by Drummond and Park [2] who showed that, after induction of anaesthesia with thiopentone and suxamethonium, 70 % of patients had an Sp_{O_2} less than 90 % after apnoea of 1 min duration when no supplementary oxygen was given.

Until the point when hand ventilation was established with a face mask in the patients in group D, there was no difference in Sp_{O_2} values compared with those in group A. It may be that the five positive pressure breaths prevented both initial hypoxaemia and further hypoxaemia, by providing partial denitrogenation. The median value for the least Sp_{O_2} in group D was 93 %. Nineteen of the 25 patients in group D (76 %) demonstrated a decrease in Sp_{O_2}, and in nine (36 %) the decrease was to less than 90 %. In most instances, the decrease occurred before the establishment of effective hand ventilation rather than during LMA placement. The mean time to establish a satisfactory airway was significantly longer in group D (table IV), as may be expected from the additional time required to administer the five tidal volume breaths before LMA insertion in this group.

Breathing 100 % oxygen for 3 min at normal tidal volume via an anaesthetic face mask with a carefully applied seal remains the standard method of denitrogenation. This has been shown to achieve 95 % denitrogenation [9], providing that an airtight seal is maintained throughout. The longer the period of preoxygenation, the greater the potential for an imperfect seal, with re-introduction of nitrogen [10]. Denitrogenation by a patient holding a face mask over the face during induction of anaesthesia is likely to be incomplete, but may be more acceptable to the patient. Some anaesthetists are reluctant to preoxygenate a patient's lungs routinely, because of inducing anxiety.

This study has demonstrated that partial denitrogenation provided sufficient oxygen reserves in healthy patients to prevent hypoxaemia during induction of anaesthesia with propofol and fentanyl and insertion of an LMA. This is in accord with the findings of Drummond and Park, who used thiopentone as the induction agent, but without an LMA [2]. Clearly, even a few breaths of oxygen-enriched air significantly increase oxygen stores. Nitrogen washout with reciprocal oxygen washin follows an exponential pattern in patients breathing 100 % oxygen. Therefore, it may be expected that, in a patient with normal lung mechanics, partial denitrogenation with 100 % oxygen may result in an initial rapid increase in oxygen reserve. The increase in oxygen reserve occurring when oxygen-enriched air is used for partial denitrogenation is less predictable.

The performances of the Datex Satlite and the Critikon Oxyshuttle pulse oximeters used in this study have been assessed elsewhere [11–13]. Most pulse oximeters have a mean error of less than 2 % at normal saturations and perfusion conditions [13]. Some models, including those used here, have a tendency to read 99–100 % at an Sp_{O_2} of 97.5 % [13]. This does not influence our findings, as both the models used have been shown to be accurate when the oxygen saturation is less than 97 % [11–13].

In conclusion, we recommend that either partial or full denitrogenation is performed in all patients in whom anaesthesia is to be induced with fentanyl and propofol with subsequent LMA insertion. Manual ventilation at induction of anaesthesia was not effective in preventing hypoxaemia.

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DOES GLYCINE ANTAGONISM UNDERLIE THE EXCITATORY EFFECTS OF METHOHEXITONE AND PROPOFOL?

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SUMMARY

We have investigated the pharmacological basis of CNS excitation that occurs in association with general anaesthesia in mice. Propofol produced sustained clonic movements during anaesthesia. Methohexitone produced intermittent non-rhythmic jerking during anaesthesia. Ethanol and pentobarbitone produced anaesthesia without associated clonic movements. Doses of all anaesthetic drugs were equipotent. Surface EEG recordings showed paroxysmal discharges consistent with interictal manifestations of cortical seizures with methohexitone or propofol, but not with ethanol or pentobarbitone. Strychnine, a glycine antagonist without effects on the cerebral cortex, and bicuculline, a $GABA_A$ *antagonist with effects on the cerebral cortex, were used in doses that were equipotent—0.5 log units less than the* ED_{10} *for clonic convulsions. Strychnine potentiated both excitatory behaviour and EEG paroxysmal discharges when given with methohexitone or propofol, but not with ethanol or pentobarbitone. Bicuculline did not affect either behaviour or EEG with any of the anaesthetic drugs. Our data show that methohexitone and propofol produced CNS excitation, while pentobarbitone and ethanol did not. We propose that the pharmacological basis of this excitation may be glycine antagonism occurring in subcortical structures.*

KEY WORDS

Anaesthetics, intravenous; methohexitone, propofol. Complications: excitatory phenomenon.

The relationship between general anaesthesia and seizures is unclear. Seizures in man have been reported in association with several general anaesthetic drugs, including methohexitone [1] and propofol [2]. It is not certain if all these reports of tonic/clonic movements in man were true seizures because EEG documentation was generally unavailable. In addition, some anaesthetic drugs that produce CNS excitation also have anticonvulsant properties in some experimental models of epilepsy [3].

We have attempted to explore the pharmacological basis of so-called seizures that occur with anaesthetic drugs. We chose two anaesthetic drugs that have been associated with CNS excitation (methohexitone and propofol). In addition, we chose two anaesthetic drugs that did not produce signs of CNS excitation in previous studies [4]. We then chose two convulsant drugs with known mechanisms of action (bicuculline and strychnine). These were given at subconvulsant doses to mice that had been given one of the four anaesthetic agents.

MATERIALS AND METHODS

Male albino mice (TO) 25–30 g were used in all experiments.

Behavioural studies

In order to achieve equipotency of anaesthetic drugs, dose–response curves were constructed. Groups of six to 10 mice were give a single dose of the anaesthetic drug i.p. Mice were assessed every 5 min for loss of righting reflex. At least four separate doses were used for each anaesthetic and dose–response curves were generated by probit transformation [5]. Equipotent doses were those that produced ED_{90} for loss of righting reflex 5 min after i.p. administration—the time to peak effect of each of the anaesthetic drugs. Equipotent anaesthetic doses were: methohexitone 52 mg kg^{-1}, propofol 125 mg kg^{-1}, pentobarbitone 32 mg kg^{-1} and ethanol 3.8 g kg^{-1}. Every 5 min after anaesthetic injection, mice were assessed for loss of righting reflex and the presence of excitatory behaviour, assessed as present, if clonic or tonic movements occurred during the 60-s period of assessment, or absent; it was not graded. Body temperature was maintained at 36–37 °C.

We used subconvulsant doses of two chemical convulsants with known mechanisms of action: bicuculline is a potent $GABA_A$ antagonist with actions in the cerebral cortex [6]; strychnine is a potent glycine antagonist with actions at subcortical nuclei and at anterior motoneurones [7], but without effects in the cerebral cortex. Mice in groups of up to 10 were given a dose of one of the chemical convulsants i.p. A dose–response curve for seizures was constructed from at least four separate doses of each drug, and the dose–response curves analysed by probit analysis. Equipotent doses of bicuculline

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(1.1 mg kg^{-1}) and strychnine (0.3 mg kg^{-1}) were those that were 0.5 log units less than the ED_{10} for clonic convulsions. These doses by themselves did not produce any alteration in murine behaviour.

Mice in groups of eight to 10 were given the ED_{90} dose of the anaesthetic. Five minutes later one group was given either strychnine or bicuculline and concurrent anaesthetic controls were given a vehicle injection. Behavioural assessment of both loss of righting reflex and CNS excitation were made every 5 min until mice had recovered (about 30 min). Comparisons between each group were made by analysis of variance over the whole time course of the experiment.

EEG experiments

Mice were anaesthetized with halothane and 66 % nitrous oxide in oxygen via a face mask. Tracheotomy was performed and an 18-gauge cannula inserted into the trachea. Anaesthesia was maintained using 1.0 % halothane and nitrous oxide in oxygen via a T-piece. Intermittent positive pressure ventilation was provided at 60 b.p.m. by a Harvard ventilator which acted as a T-piece occluder. Body temperature was maintained at 36–37 °C. Surface EEG was recorded via a pair of 2-mm silver–silver chloride electrodes inserted 1 cm apart subcutaneously immediately above the cranium. An earth electrode was inserted into the nostril. The surface EEG signal was taken via Medelec Biological amplifiers to a Gould recorder, with a measured frequency response flat to 120 Hz, and also to an analog–digital converter for storage on computer hard disc. Analysis of the signal was from raw EEG. After the electrodes were inserted, vecuronium 0.2 mg kg^{-1} was injected i.p., halothane discontinued and anaesthesia maintained with 66 % nitrous oxide in oxygen. Five minutes was allowed to wash out residual halothane.

A baseline EEG was then recorded for 60 s. Immediately after this, the anaesthetic drug was injected and 60-s recordings made every 5 min up to 30 min. As this time corresponded to the time of recovery from anaesthesia, the experiment was stopped after 30 min by the reintroduction of 5 % halothane inspired concentration. A final EEG was recorded 1–2 min later when the EEG was completely flat. This gave a measure of the noise in the system.

The effects on the EEG signal of the anaesthetic drugs alone were compared with the anaesthetic drugs in combination with strychnine and bicuculline. Comparison between each group was made by Mann–Whitney *U* test at each 5-min interval and by analysis of variance over the whole course of the study.

RESULTS

Behaviour

Propofol anaesthesia was associated with seizure-like clonic movements in up to 85 % of mice. These clonic movements occurred in all four limbs, the tongue and the face, and lasted from 5 to 20 min. Clonic movements generally occurred during the period of anaesthesia, but would occasionally outlast the loss of righting reflex. All mice made a full recovery and returned to normal murine activities. There did not appear to be a post-ictal phase of inactivity.

While clonic movements were not observed in association with methohexitone anaesthesia, there were spontaneous non-rhythmic jerking movements of short duration (< 1 s) in up to 50 % of mice on induction and recovery from anaesthesia. Smooth induction and recovery occurred with ethanol and pentobarbitone and there were no associated jerking or clonic movements.

When strychnine 0.3 mg kg^{-1} was given 5 min after propofol, the incidence of anaesthesia was not altered, but the incidence of the clonic seizure-like movements was increased significantly. When bicuculline 1.1 mg kg^{-1} was give 5 min after propofol, neither the incidence of anaesthesia nor the incidence of seizure-like clonic movements was altered (table I).

The incidence of anaesthesia was unaltered when strychnine was give 5 min after methohexitone. However, while seizure-like clonic movements did not occur with methohexitone alone, there was a significant increase in incidence when strychnine was added. Bicuculline did not affect either the incidence of anaesthesia or the incidence of clonic movements when give 5 min after methohexitone (table I).

When strychnine or bicuculline was given after either ethanol or pentobarbitone, there was no alteration in the incidence of anaesthesia. There were no signs of any clonic activity with ethanol or pentobarbitone, either alone or in conjunction with strychnine or bicuculline (results not shown).

Neither strychnine 0.3 mg kg^{-1} nor bicuculline 1.1 mg kg^{-1} produced any overt behavioural change.

EEG

Surface EEG from mice given propofol or methohexitone showed high amplitude paroxysmal dis-

TABLE I. *Effects of strychnine and bicuculline on the incidence of seizure-like clonic movements in mice anaesthetized with propofol 125 mg kg^{-1} i.p. or methohexitone 52 mg kg^{-1}, as numbers out of the total. Bicuculline and strychnine were given 5 min after the anaesthetic drug. *$P < 0.05$ compared with vehicle-treated concurrent controls (ANOVA)*

	Time (min)					
Drug	5	10	15	20	25	30
Propofol 125 mg kg^{-1}						
Vehicle	4/11	4/11	2/11	1/11	2/11	0/11
Bicuculline 1.1 mg kg^{-1}	6/11	5/11	5/11	3/11	0/11	0/11
Strychnine 0.3 mg kg^{-1}	6/11	7/11	7/11	6/11	4/11	2/11*
Methohexitone 52 mg kg^{-1}						
Vehicle	0/8	0/8	0/8	0/8	0/8	0/8
Strychnine 0.3 mg kg^{-1}	0/8	2/8	4/8	2/8	2/8	1/8*
Vehicle	0/6	0/6	1/6	0/6	0/6	0/6
Bicuculline 1.1 mg kg^{-1}	0/6	0/6	0/6	0/6	0/6	0/6

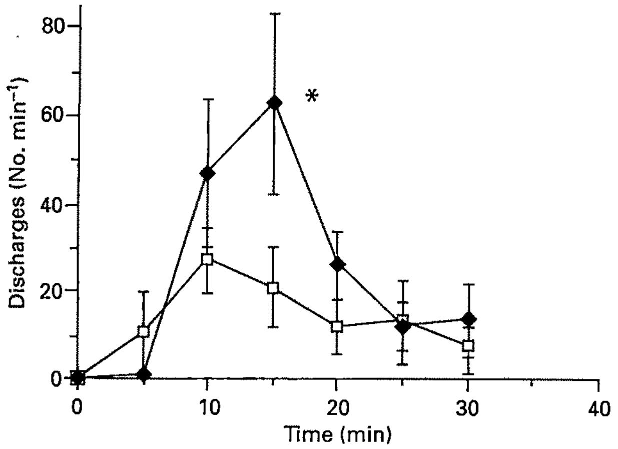

FIG. 1. Effects of strychnine 0.3 mg kg^{-1} on the number of paroxysmal EEG discharges per minute associated with propofol 125 mg kg^{-1} (mean, SEM). Mice were given propofol 125 mg kg^{-1} at 0 min. After the 5-min EEG recording, one group (◆, $n = 5$) were given strychnine 0.3 mg kg^{-1} i.p. and the other group (□, $n = 6$) were given the vehicle injection. Strychnine significantly increased the numbers of EEG discharges per minute compared with controls (*$P < 0.05$; Mann–Whitney *U* test).

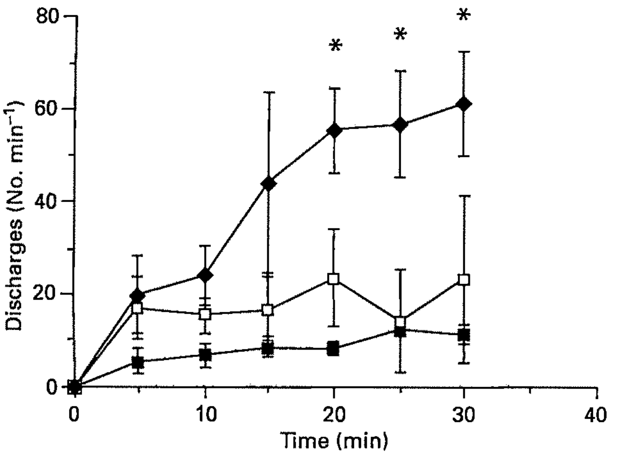

FIG. 2. Effects of strychnine and bicuculline on paroxysmal EEG discharges per minute associated with methohexitone 52 mg kg^{-1} (mean, SEM). All mice were given methohexitone at 0 min. After the 5-min EEG recordings, one group (◆, $n = 5$) were given strychnine 0.3 mg kg^{-1} i.p., another group (■, $n = 5$) were given bicuculline 1.1 mg kg^{-1} and the control group (□, $n = 5$) were given the vehicle injection only. Strychnine, but not bicuculline, significantly increased the numbers of EEG discharges per minute compared with controls (*$P < 0.05$; Mann–Whitney *U* test).

charges. Discharges of 20–70 ms duration were described as spikes, and those of 70–200 ms duration were described as sharp waves [8], if the amplitude exceeded twice the measured baseline. As there was no reason to discriminate between spikes and sharp waves on functional grounds, these were grouped together as paroxysmal discharges.

To assess the effects of bicuculline and strychnine on paroxysmal EEG discharges produced by propofol and methohexitone, the numbers of discharges per minute were compared (figs 1, 2). Strychnine significantly ($P < 0.05$) increased the numbers of EEG paroxysmal discharges per minute associated with propofol and methohexitone. Strychnine alone did not affect the surface EEG. The combination of strychnine and pentobarbitone or ethanol did not result in any EEG paroxysmal discharges (results not shown). On the other hand, bicuculline at a dose equipotent with strychnine, did not alter the incidence of EEG paroxysmal discharges associated with methohexitone anaesthesia.

DISCUSSION

Two of the anaesthetics investigated, methohexitone and propofol, produced signs of CNS excitation, while two others, ethanol and pentobarbitone, did not. While excitatory side effects of methohexitone are well recognized [1], the excitatory properties of propofol are confined to individual case reports [2]. We report here that propofol had marked effects on behaviour, resulting in clonic movements that were often sustained into the recovery period. This is in contrast with the initial preclinical reports in which propofol was described as providing smooth induction and recovery from anaesthesia in mice [9]. The probable explanation for the failure to observe excitatory effects in the studies reported initially was that propofol was given i.v. to provide anaesthesia of brief duration, while in our study doses given i.p. resulted in anaesthesia lasting up to 30 min, and would have resulted in more sustained anaesthetic concentrations in the brain. When we injected mice with small doses i.v. we observed transient excitatory effects in some mice; these effects, if present, were mild and not sustained in the manner we observed using the i.p. route.

Both propofol and methohexitone produced similar EEG patterns, characterized by spikes and sharp waves (paroxysmal discharges). The occurrence of paroxysmal discharges on surface EEG with propofol and methohexitone, but not with ethanol and pentobarbitone, suggested that these EEG changes were related to behavioural excitation. It was not possible with this technique to observe behavioural and EEG changes simultaneously, as mice were given a neuromuscular blocking drug when EEG was recorded. Methohexitone did not produce clonic movements alone, but only when combined with a subconvulsant dose of strychnine. We are unable to explain why propofol and methohexitone showed similar EEG patterns but different behavioural patterns.

EEG paroxysmal discharges similar to those in our experiments have been shown to be associated with depolarizing shifts recorded from intracellular electrodes [10]. Paroxysmal depolarization shifts are considered as the typical, most characteristic epileptiform expression of the neurone. However, we have been careful not to label the behavioural and EEG phenomena that we have observed as seizures. We have described the behaviour as sustained clonic movements, and the EEG is best described as interictal. However, both behavioural and EEG changes are clearly excitatory.

Hypocapnia (and repetitive hand clapping) has been shown to elicit seizure patterns in the EEG in the presence of enflurane [11]. In our experiments, EEG recordings were performed on mice undergoing ventilation and no attempt was made to control Pa_{CO_2}. While we cannot exclude the possibility that hypocapnia may have been present, the same pattern of ventilation was used for all experiments, regardless of the drug treatment. In mice given injections of vehicle alone or subconvulsant doses of strychnine or bicuculline, there was no evidence of excitatory phenomena on the EEG. Also, there were no signs of excitatory effect on EEG recorded under ethanol or pentobarbitone anaesthesia. These results suggest that hypocapnia was unlikely to be having a significant effect in these experiments.

The observation that strychnine augmented the behavioural and EEG signs of excitation caused by methohexitone and propofol, while bicuculline did not, may provide us with some insight into the mechanism of excitation. Strychnine is a specific glycine antagonist (K_i 5–10 nmol litre^{-1}) [12]. While glycine is a ubiquitous amino acid in the central nervous system, its role as an inhibitory neurotransmitter appears confined to subcortical areas [13]. In rats, specific strychnine binding was greatest in the spinal cord and in the medulla oblongata–pons area, while lesser amounts of binding occurred in the hypothalamus and thalamus. The cerebral cortex was devoid of binding [7]. The distribution of strychnine binding sites in human brain is comparable to that in rat brain, with high densities in the pons, medulla and upper spinal cord [14]. Bicuculline is a high affinity $GABA_A$ antagonist. In common with glycine, GABA acts as an inhibitory neurotransmitter in the mammalian central nervous system. However, as a neurotransmitter GABA (but not glycine) acts in the cerebral cortex. Both act as neurotransmitters on the spinal cord. Bicuculline has been shown to produce seizures via actions on the cortex [6]. Our results suggest that propofol and methohexitone may be producing excitatory effects via actions that are similar to those of strychnine—that is, via glycine antagonism at a subcortical level. It is not clear if the proposed glycine antagonism by propofol and methohexitone is a result of direct pharmacological antagonism. Surface EEG recordings are, most probably, detecting cortical electrical activity. The sensitivity of the EEG paroxysmal discharges to strychnine suggests that glycine antagonism may be allowing subcortical groups of neurones to undergo synchronous firing, leading to cortical seizure activity.

Demonstration of simple glycine antagonism may be useful for screening novel anaesthetic compounds, if the excitatory effects of anaesthetic were considered undesirable, as has been suggested [11]. The question of whether or not excitatory effects of anaesthetic drugs could be considered as potentially harmful has not been addressed in these experiments. There is evidence to suggest that cerebral seizures are not innocuous, even in the absence of motor manifestations [15]. The question of the possible deleterious effects of propofol and methohexitone on brain function remains unresolved.

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SHORT COMMUNICATIONS

EFFECT OF DOXAPRAM ON THE RATE OF RECOVERY FROM ATRACURIUM AND VECURONIUM NEUROMUSCULAR BLOCK

R. COOPER, G. McCARTHY, R. K. MIRAKHUR AND V. R. MADDINENI

SUMMARY

We have studied the effect of doxapram on the rates of spontaneous and neostigmine-induced recovery from neuromuscular block with atracurium and vecuronium, by measurement of the time to recovery of T1 (first twitch in the train-of-four) from 25 to 75% of control (recovery index, RI). After each neuromuscular blocking drug, RI was measured without administering either doxapram or neostigmine (control group), or after administration of doxapram 1 mg kg^{-1}, neostigmine 50 µg kg^{-1} or a combination of doxapram and neostigmine, in groups of 10 patients. RI was significantly longer after vecuronium in the presence of doxapram compared with control (20.1 min vs *14.6 min). There was no significant difference in the RI after atracurium in the presence of doxapram compared with control (12.5 min* vs *11.8 min) or when neostigmine was administered with or without doxapram (2.4 min* vs *2.4 min, respectively after vecuronium; 3.3 min* vs *2.9 min, respectively, after atracurium).*

KEY WORDS

Neuromuscular relaxants: atracurium, vecuronium. Analeptics: doxapram. Interactions.

The analeptic agent, doxapram, is often used at the end of anaesthesia to stimulate ventilation and accelerate recovery from the effects of volatile anaesthetic agents without antagonizing analgesia [1, 2]. A recent experimental study has demonstrated that it may enhance a partial neuromuscular block by agents such as tubocurarine [3]. This is clinically important as doxapram is often administered when residual neuromuscular block may still be present. The purpose of this study was to examine the effect of doxapram on neuromuscular transmission by measuring the recovery index in patients given vecuronium or atracurium—the two neuromuscular blockers which currently are in most common use [4].

METHODS AND RESULTS

We studied 80 adult patients aged 18–70 yr (ASA I or II) with their informed consent and the approval of the Regional Medical Ethics Committee. Patients with obesity, renal or hepatic dysfunction, or receiving any drugs known to interact with neuromuscular blocking agents were excluded from study.

All patients were premedicated with oral diazepam 10 mg 60–90 min before surgery. Anaesthesia was induced with fentanyl 1–2 µg kg^{-1} and thiopentone 3–5 mg kg^{-1} and maintained with 70% nitrous oxide and 0.5% halothane in oxygen; increments of fentanyl 0.5–1.0 µg kg^{-1} were administered as required. ECG, non-invasive arterial pressure, temperature, end-tidal carbon dioxide concentration and oxygen saturation were monitored. Ventilation was adjusted to an end-tidal carbon dioxide concentration of 4.5–5%.

The ulnar nerve was stimulated percutaneously at the wrist after induction of anaesthesia with supramaximal stimuli of 0.2 ms duration, in a train-of-four (TOF) mode at 2 Hz every 10 s, and the resultant force of contraction of the adductor pollicis muscle measured and recorded using a force displacement transducer and neuromuscular function analyser (Myograph 2000, Biometer Ltd). When control responses had stabilized, 40 patients received vecuronium 80 µg kg^{-1} and the other 40 atracurium 450 µg kg^{-1} (approximately 2 × ED_{95} doses). Additional increments of the agent were given at T1 (first response in the TOF) 20% of control according to the duration of surgery. Within each group of 40, when the T1 had recovered to 25% of control, groups of 10 patients received doxapram 1 mg kg^{-1} (group I), neostigmine 50 µg kg^{-1} and doxapram 1 mg kg^{-1} (group II), neostigmine 50 µg kg^{-1} (group III) or saline (group IV, control group). Patients receiving neostigmine also received glycopyrronium 10 µg kg^{-1}. The allocation to these groups and to neuromuscular blocking drug was randomized. The time taken for T1 to recover from 25 to 75% of control (recovery index, RI) was recorded and used to measure the speed of recovery. TOF ratios at T1 75% were recorded also. The study was discontinued at this stage and the patient managed appropriately.

With each blocking drug, the groups receiving neostigmine were compared with each other, as were the groups who did not receive neostigmine. The results were subjected to analysis of variance and the Tukey HSD modification of the analysis of variance to determine statistical significance.

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TABLE I. *Patient characteristics and neuromuscular data (mean (range or* SD*)). RI = Recovery index.* *$P < 0.05$ *compared with group IV (control) receiving vecuronium and groups I and IV receiving atracurium*

	Group I Doxapram	Group II Doxapram/ neostigmine	Group III Neostigmine	Group IV Control (saline)
Atracurium				
Age (yr)	37 (20–68)	41 (25–63)	38 (21–61)	49 (20–65)
Weight (kg)	74 (11)	70 (15)	66 (12)	67 (10)
Sex (M/F)	7/3	7/3	5/5	5/5
RI (min)	20.1 (6.8)*	2.4 (1.2)	2.4 (1.7)	14.6 (4)
TOF at T1 75 %	42 (8)	62 (10)	61 (8)	42 (13)
Vecuronium				
Age (yr)	53 (33–64)	46 (22–65)	47 (24–64)	47 (24–63)
Weight (kg)	69 (9)	74 (11)	67 (12)	69 (13)
Sex (M/F)	5/5	4/6	4/6	5/5
RI (min)	12.5 (3.7)	3.3 (1)	2.9 (1.2)	11.8 (3.6)
TOF at T1 75 %	36 (9)	62 (16)	57 (19)	47 (14)

The patients in the eight groups were comparable in physical characteristics (table I). RI in the vecuronium group which received doxapram was significantly greater ($P < 0.05$) compared with the control (saline) group (20.1 min *vs* 14.6 min; mean difference 5.5 min, 95 % confidence limits of the difference 0.26–10.74 min). RI was not significantly different between groups to whom neostigmine was administered (2.4 min in both groups). After atracurium, RI was not significantly different between groups receiving neostigmine (3.3 min and 2.9 min) or in spontaneously recovering groups with or without doxapram (12.5 min *vs* 11.8 min). There was no significant difference in the TOF ratios at T1 75 % in both neuromuscular blocker groups with or without doxapram, although the ratios were significantly greater in the groups given neostigmine (table I).

COMMENT

The results of this study suggest that a single dose of doxapram 1 mg kg^{-1} significantly prolonged spontaneous recovery from neuromuscular block induced by vecuronium but not that with atracurium. Recovery induced by neostigmine was not affected in the present study, although it has been observed elsewhere [5].

Pollard, Randall and Pleuvry [3] suggested from an *in vitro* study that doxapram enhanced the neuromuscular block produced by agents with relatively greater presynaptic effect. The results of the present study do not support this contention, as vecuronium has been reported to have a relatively lesser presynaptic effect than atracurium during the onset of block [6]. In any case, there is no evidence to suggest that vecuronium has greater presynaptic effect than atracurium. Doxapram may be affecting the uptake of vecuronium by the liver, but this is speculative. However, if this were the reason then atracurium, which is less dependent upon liver for termination of its action, would be less affected, as in the present study. At present the reason for the interaction between doxapram and vecuronium remains unclear.

Our findings differ from those of Pollard and Orlowski [5], who demonstrated that antagonism of vecuronium-induced neuromuscular block by neostigmine was retarded in the presence of a single bolus dose of doxapram 0.5 mg kg^{-1}. There was no such inhibition in the presence of neostigmine in the present study, but this may be the result of the use of a larger dose of doxapram in our study. A direct comparison cannot be made with the former study, as it did not assess the effect of doxapram on the rate of spontaneous recovery from vecuronium block.

In summary, a single dose of doxapram 1 mg kg^{-1} prolonged the rate of spontaneous recovery from a vecuronium-, but not atracurium-induced neuromuscular block. Neostigmine-induced recovery was unaffected. Although the differences in the present study were relatively small, they may be clinically important in situations in which neuromuscular block is not adequately antagonized or when larger doses of vecuronium are used.

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ESMOLOL HYDROCHLORIDE FOR MANAGEMENT OF THE CARDIOVASCULAR STRESS RESPONSES TO LARYNGOSCOPY AND TRACHEAL INTUBATION

M. VUCEVIC, G. M. PURDY AND F. R. ELLIS

SUMMARY

In a double-blind, randomized, controlled prospective study, 30 grade ASA I/II patients received a continuous i.v. infusion of normal saline or esmolol hydrochloride before induction of anaesthesia and tracheal intubation. Arterial pressure and heart rate were measured to assess the pressor response to laryngoscopy and intubation. The heart rate decreased in the esmolol group before induction of anaesthesia. The pressor response to laryngoscopy was significantly less marked in the esmolol group.

KEY WORDS

Intubation, tracheal: cardiovascular response. Sympathetic nervous system: β-adrenergic antagonists, esmolol.

Laryngoscopy and tracheal intubation frequently induce a cardiovascular stress response, characterized by hypertension, tachycardia and increased serum concentrations of catecholamines [1]. This sympathoadrenal response to laryngoscopy results in an increase in cardiac workload which, in turn, may culminate in perioperative myocardial ischaemia and acute heart failure in susceptible individuals [2]. This response is undesirable in any patient with heart disease undergoing surgery, irrespective of the nature of surgery.

Esmolol hydrochloride is a relatively new cardioselective, i.v. beta adrenoceptor antagonist. It has a rapid onset of action, exerts a peak haemodynamic effect within minutes and possesses a short elimination half-life of 9 min [3]. Consequently, it should prove ideal for control of the short-lived haemodynamic sequelae associated with laryngoscopy and intubation [1].

This study was undertaken to compare the haemodynamic effects of laryngoscopy and tracheal intubation during an infusion of esmolol or an infusion of placebo (normal saline) in anaesthetized ASA I/II patients.

METHODS AND RESULTS

After obtaining hospital Ethics Committee approval and written, informed consent, we studied 30 ASA I/II patients undergoing laryngoscopy and intubation for elective abdominal surgery.

All patients were premedicated with diazepam 0.15 mg kg^{-1} orally 2 h before operation. An 18-gauge i.v. cannula was inserted under local anaesthesia into a peripheral vein and a continuous i.v. infusion of esmolol or normal saline was administered for 10 min before the induction of anaesthesia. Patients in the study group received esmolol 500 $\mu g\ kg^{-1}\ min^{-1}$ for 2 min as a loading dose and thereafter a maintenance infusion of 100 $\mu g\ kg^{-1}\ min^{-1}$. This infusion was maintained for 5 min after tracheal intubation unless significant bradycardia (50 beat min^{-1} or less), hypotension (systolic arterial pressure 90 mm Hg or less, or $> 30\%$ decrease from baseline), or both occurred. The control group received only normal saline.

After 10 min, anaesthesia was induced with thiopentone 5 mg kg^{-1} and suxamethonium 1.5 mg kg^{-1} was given to facilitate tracheal intubation. After manual ventilation of the lungs with 100% oxygen for 30–60 s, laryngoscopy and tracheal intubation were performed by the same investigator on each occasion and the duration of laryngoscopy noted. After intubation, the lungs were ventilated manually with 66% nitrous oxide and 1% isoflurane in oxygen until spontaneous ventilation resumed. No opioid analgesics or non-depolarizing neuromuscular blocking drugs were administered during the study.

Heart rate was recorded using an ECG and systolic, diastolic and mean arterial pressure were recorded non-invasively using a Dinamap automatic pressure machine. These measurements were made at 1-min intervals during the infusion period, but at 30-s intervals during laryngoscopy and intubation. Any deleterious cardiovascular events were noted.

Parametric data, including weight, baseline heart rate and arterial pressure were compared using unpaired Student's *t* test. Changes in heart rate, arterial pressure and rate–pressure product were analysed also using unpaired Student's *t* test and these were validated by analysis of covariance.

There were no significant differences between the two groups in age and weight. In addition, there were no significant differences between the two groups in the two principal response variables (systolic arterial pressure and heart rate) before

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TABLE I. *Systolic arterial pressure (SAP) and heart rate (HR) changes (mean (SD)). RPP = Rate–pressure product. Significant differences between groups:* *$P < 0.05$; ***$P < 0.001$

	Group A (esmolol)	Group B (normal saline)
SAP (mm Hg)		
Baseline	133 (16)	139 (14)
Before induction	130 (14)	135 (14)
Maximum after intubation	151 (18)	188 (23)***
HR (beat min^{-1})		
Baseline	79 (9)	83 (13)
Before induction	68 (5)	83 (13)***
Maximum after intubation	92 (9)	110 (17)*
Maximum RPP	13393 (1820)	19947 (4750)***

commencing the i.v. infusion. During the 10-min infusion period before induction of anaesthesia there was no significant change in systolic arterial pressure in each group. However, patients in the esmolol group had a significant decline in heart rate during the pre-induction period compared with the control group ($P < 0.001$) (table I).

Several changes occurred during and immediately after laryngoscopy. Both groups developed similar and significant increases in heart rate ($P < 0.001$), but the maximum heart rates in the study group were significantly less than those recorded in the control group ($P < 0.05$). In addition, the maximum pressures recorded in the control group were significantly greater than those recorded in the study group ($P < 0.05$). The maximum rate–pressure products were consistently and significantly increased in the control group compared with the study group ($P < 0.001$) (table I). In the esmolol group the rate–pressure product exceeded 15000 in only one patient and this was associated with the only prolonged and difficult laryngoscopy.

Overall, the duration of laryngoscopy and intubation was similar in both groups and on only one occasion was difficulty encountered and laryngoscopy exceeded 60 s. On no occasion was bradycardia or hypotension encountered which would have necessitated discontinuation of the study.

COMMENT

The major finding of this study is that the maximum rate–pressure product recorded in association with laryngoscopy and tracheal intubation was reduced significantly in patients who received an infusion of esmolol hydrochloride. In addition, the regimen of esmolol used in this study did not result in any deleterious sequelae associated with beta adrenergic block.

Several techniques have been used with varying degrees of success to obtund the pressor response to laryngoscopy and intubation including i.v. or topical lignocaine, thoracic extradural analgesia, i.v. opioids and peripheral vasodilators. However, none of these techniques has gained widespread acceptance.

Current beta blockers have a relatively long duration of action and, in some cases, lack cardioselectivity. Esmolol possesses several properties which suggest that it might be valuable in obtunding responses to laryngoscopy and intubation. First, it is a highly cardioselective agent, analogous to metoprolol, and so is unlikely to induce bronchospasm. Second, it undergoes rapid esterase-mediated metabolism, characterized by an elimination half-life of 9.2 min and a total body clearance of 285 ml min^{-1}, culminating in a rapid offset of action when the infusion is discontinued [3]. Finally, significant drug interactions have not been reported yet and the only adverse effects reported, thus far, have been hypotension and thrombophlebitis at the site of injection. The latter sequela may be avoided by careful dilution of the agent (5 mg ml^{-1}) and the judicious use of doses.

Esmolol has been administered, with success, as a bolus injection to obtund the pressor response to laryngoscopy [4]. We preferred to use an infusion as it was felt this would be less likely to cause acute hypotension and bradycardia. In addition, an infusion enabled us to record the effects of esmolol before stimulation.

A rate–pressure product greater than 15000, which is considered undesirable in patients with coronary artery disease, was recorded in only one patient in the study group, who was subjected to the only prolonged laryngoscopy [5]. However, only two patients in the control group recorded a maximum product less than 15000. In both groups the cardiovascular response was instantaneous, peaking within 2 min of intubation in all patients, and was transient. This finding is consistent with the results of other authors [6].

It is the opinion of the authors that the anaesthetic technique used here, although widespread, is inappropriate in patients with significant cardiorespiratory disease and hence only ASA grade I/II patients were studied. We conclude that a continuous i.v. infusion of esmolol hydrochloride is a safe and effective technique for suppressing the cardiovascular stress response associated with laryngoscopy and intubation.

ACKNOWLEDGEMENTS

The authors acknowledge the assistance of Mr A. Rees of Hull University who carried out statistical analysis of the data.

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REFLECTIVE BLANKETS USED FOR REDUCTION OF HEAT LOSS DURING REGIONAL ANAESTHESIA

K. B. HINDSHOLM, C. BREDAHL, P. HERLEVSEN AND P. K. KRUHØFFER

SUMMARY

We have studied the ability of reflective blankets to reduce net loss of body heat during regional anaesthesia for total hip arthroplasty. Thirty patients were allocated randomly to either the study group (insulated with reflective blankets) or the control group (no reflective blankets). Surgical and operation room draping, theatre temperature and i.v. fluid administration were standardized for all patients. Total body heat was deduced from core temperature (aural canal) and mean skin temperature (four measuring sites). After 2 h of surgery, loss of body heat was reduced significantly in patients wrapped in reflective blankets (26 kJ) compared with those in the control group (95 kJ).

KEY WORDS

Temperature: body. Anaesthetic techniques: extradural, spinal. Equipment: reflective blanket. Surgery: hip arthroplasty.

Loss of body heat during both general and regional anaesthesia is a common problem. When heat loss exceeds metabolic heat production, the patient may become hypothermic (core temperature < 36 °C). The adverse effects and risks of allowing an anaesthetized patient to cool have been emphasized recently by Imrie and Hall [1]. There is some controversy regarding the heat conserving capacity of reflective blankets during general anaesthesia for neurosurgical procedures [2–4]. In only one of these studies was heat balance rather than core temperature considered [4]. In this study, a reduction in net heat loss was found in patients wrapped in reflecting blankets.

The ability of reflecting blankets to reduce net loss of body heat has not previously been evaluated during regional anaesthesia. Although central thermoregulation remains intact during regional anaesthesia, abnormal heat loss occurs because of redistribution of heat from the core to the periphery, increased skin blood flow resulting from sympathetic block, reduced hormonal response to surgical stimulation and impairment of shivering in the area of the block [1].

The present study was designed to assess the heat conserving capacity of reflecting blankets during regional anaesthesia for total hip arthroplasty.

METHODS AND RESULTS

We studied 30 patients (13 female), ASA class I or II, undergoing elective total hip arthroplasty for osteoarthritis. Informed consent was obtained from each patient and the study was approved by the District Ethics Committee.

Patients were allocated randomly to either the study group (insulated with reflective blankets as detailed below) or the control group (no reflective blankets). The two groups were comparable in age (range 43–82 yr), weight (range 45–90 kg), height (range 150–183 cm), and rectal temperature on the morning of operation (range 36.5–37.4 °C). Surgical draping was identical in both groups. In addition, all patients wore a cotton gown and were covered as completely as possible with a standard operating room draping—three weave cotton blankets. In the anaesthetic room, patients in the study group were wrapped additionally in reflecting blankets (Sun-Flex aluminized plastic sheetings) leaving only the head, fingers and operating field uncovered.

All patients received the same anaesthetic technique. Premedication consisted of diazepam 5–20 mg orally according to age. On arrival in the anaesthetic room, the patient received 500 ml of isotonic sodium chloride (37 °C) i.v. Subsequently, combined spinal–extradural analgesia was performed, using a "single space technique". Subarachnoid puncture was performed via the L2–3 or L3–4 interspace and 0.5% plain bupivacaine 3.0 ml was injected. The level of sensory block was assessed 15 min later. The analgesic level was defined as the upper dermatomal level with diminished sensation to pinprick. Extradural 2% lignocaine 4.0 ml was administered 90 min after the induction of spinal analgesia and repeated every 30 min for the remainder of the operation period.

All patients underwent surgery in the same operating theatre, where the ambient temperature was maintained at 21 °C with air renewal 20 times per hour. All blood and i.v. fluid infusions were heated to 37 °C. Throughout operation, dry oxygen 3 litre min^{-1} was given by nasal catheter.

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Core temperature was measured in the aural canal. Peripheral temperature was measured on four sites: lateral upper arm (Ta), nipple (Tn), anterior mid-thigh (Tt) and lateral mid-calf (Tc). Central and peripheral temperatures were recorded every 15 min during surgery using an electronic thermometer (type CTD-25 Ellab A/S, Copenhagen). All probes were fast reacting (type MEA-22130-A and MHF-18058-A Ellab A/S, Copenhagen) and had been calibrated previously against a mercury-in-glass thermometer in a water bath. Accuracy was ±0.1 °C over the temperature range studied. An estimate of the mean skin temperature (MST) was calculated using the four-skin-points formula: $MST = 0.3(Tn+Ta)+0.2(Tt+Tc)$. Even though the mean skin temperature is most accurately determined using 10 or more skin temperature sites, for practical reasons the four-site system chosen was the most appropriate for this study (Holdcroft and Hall compared the 15-site method of Mitchell and Wyndham with the four-point method during both general and regional anaesthesia and found good agreement [5]). Mean body temperature (MBT) was determined from aural temperature (Tau) and MST according to the equation: $MBT = 0.66 \times Tau + 0.34 \times MST$. Total body heat (TBH) in kJ was derived using the formula: $TBH = MBT \times 3.47 \times$ body weight (kg) where 3.47 is the specific heat of the body in kJ $°C^{-1}$ kg^{-1}. Different aspects of these methods of measuring net changes in body heat have been discussed in detail elsewhere [1, 5].

For calculation of the required number of patients, the smallest difference between the groups not to be overlooked with regard to changes in core temperature was estimated to 1.00 °C and the SD to 0.75 °C. Type I error was set at 5 % and type II error at 10 %. With these assumptions, 11 patients were required in each group. The data are presented using median values and 25–75 percentiles. Comparison of the groups with regard to patient characteristics, blood loss, infusion requirements and level of sensory block after spinal analgesia was made using the Fisher exact test and Mann–Whitney rank-sum test. Changes in temperature and body heat in each group and between the groups were analysed using non-parametric two-way analysis of variance. Changes within groups at different times were analysed using the multiple comparison procedure based on the Friedmann test. The statistical computer program MEDSTAT version 2.1 (Astra, Copenhagen 1989) was used for calculations. $P < 0.05$ was considered statistically significant. Statistical analysis of the data was confined to the first 2 h of surgery because of an inadequate number of patients beyond this interval (10 patients).

The two groups were comparable for blood loss (range 300–2600 ml) and infusion requirements: isotonic sodium chloride (range 500–3000 ml), isotonic sodium–glucose (500–3000 ml), Macrodex (range 350–1000 ml) and blood transfusions (range 0–1400 ml). There was no difference between the groups in the level of sensory block after spinal analgesia (range T12–T8). Hypotension (mean arterial pressure < 66 % of the original value) was observed in two patients: one patient (study group) received one dose of ephedrine 5 mg i.v. and one patient (control group) received two doses of ephedrine 5 mg i.v. The first temperature measurement did not differ between the two groups in either aural canal temperature or MST. After 2 h of surgery, the aural temperature had decreased significantly in both groups; however, the decrease was significantly less in the study group compared with the control group. The MST increased significantly in both groups, but no difference was found between groups in the course of the MST. In both groups there was a tendency towards a decrease in TBH which became significant 105 min after the initial temperature measurement. This decrease was reduced significantly in the study group compared with that in the control group (fig.1). After 2 h of surgery, median total body heat had decreased by 26 kJ in the study group and 95 kJ in the control group ($P < 0.05$).

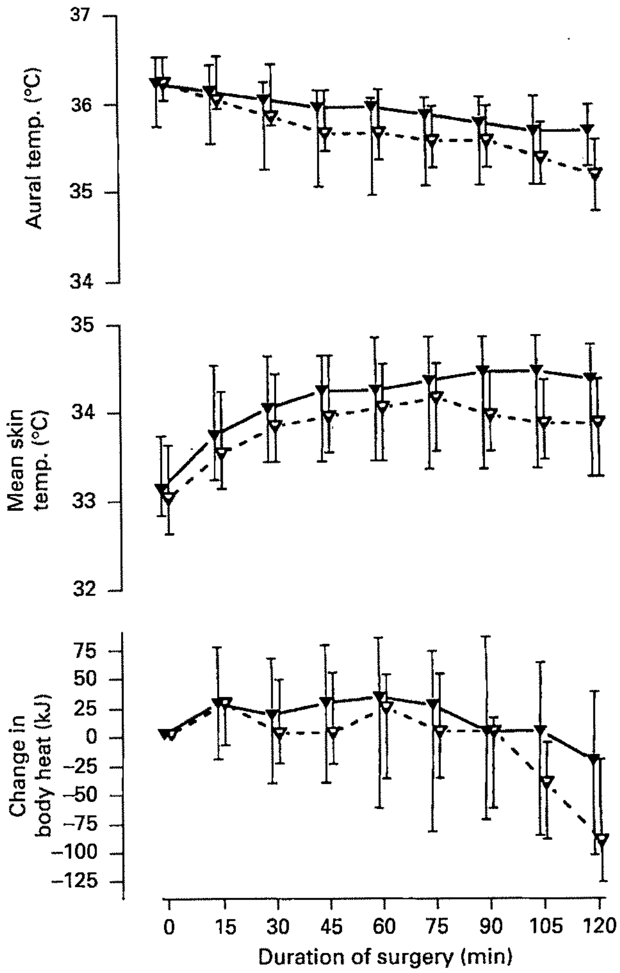

FIG. 1. Aural temperatures, mean skin temperatures and changes in body heat during surgery (median values, lower and upper quartiles). ▼ = Study group; ▽ = control group.

COMMENT

In this study, we found a decrease in core temperature throughout the whole period, but there was no change in total body heat during the first 90 min of surgery. This is a result of the associated increase in MST caused by a distribution of heat from the core to the periphery.

When the outer region of a body becomes warmer, heat loss obviously occurs more easily. To prevent this, adequate covering is necessary. The conservation of body heat in the control group was impressive, and demonstrates the importance of insulation with cotton blankets. Our results demonstrate also the additional effect of reflective blankets. These blankets comprise a metallized plastic sheeting which acts primarily by reducing the heat loss caused by radiation, but also by reducing convectional loss by minimizing draughts.

At rest, 75% of basal heat production is lost by radiation and convection from the body surface [1]. Although additional covering with reflecting blankets did not totally prevent net loss of body heat during the whole period of our study, it was reduced significantly compared with the control group. Carli, Emery and Freemantle have shown recently that the maintenance of normothermia during elective hip arthroplasty appears to attenuate protein breakdown and nitrogen loss after surgery [6]. As a major part of the protein breakdown occurs in skeletal muscles, and as protein loss may be expected to delay recovery after operation, every effort should be made to minimize thermal stress during anaesthesia.

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CASE REPORT

AIRWAY MANAGEMENT IN A CASE OF NECK IMPALEMENT: USE OF THE OESOPHAGEAL TRACHEAL COMBITUBE AIRWAY

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SUMMARY

A patient presented with neck impalement after a traffic accident. Respiratory arrest demanded immediate tracheal intubation, which was impossible as a wooden splinter had partially obstructed the pharynx and prevented laryngoscopy. An oesophageal tracheal Combitube airway was inserted successfully and the patient's lungs were ventilated adequately until tracheotomy was performed.

KEY WORDS

Airway: oesophageal tracheal Combitube, obstruction. Intubation, tracheal. Complications: cardiorespiratory arrest.

Rapid establishment of a patent airway is a primary goal of cardiopulmonary resuscitation in apnoeic patients [1]. Tracheal intubation may be difficult under some circumstances [2]. A new airway, the Combitube (Sheridan Catheter Corp., Argyle, New York, U.S.A.) may be used as an alternative when tracheal intubation has failed [3–7].

The Combitube is a plastic double-lumen tube (fig. 1). The "tracheal" channel has an open distal end, while the "oesophageal" channel is occluded at its distal end and has openings in the pharyngeal section. Depending on the position of the tube, the inflated distal cuff seals either the oesophagus or the trachea. A large balloon is inflated in the oropharynx to secure the tube in position and occlude the oral and nasal airway.

The Combitube is introduced by grasping the tongue and jaw between thumb and forefinger and guiding the device gently into the oesophagus or trachea to the indicated depth with the neck in the neutral, semiflexed position. The oropharyngeal balloon is inflated with 100 ml of air by the enclosed large syringe and the distal cuff with 10–15 ml of air.

Ventilation is started through the longer tube leading to the "oesophageal" lumen and is continued if auscultation confirms lung inflation without gastric insufflation. Air passes into the pharynx and thence into the trachea (fig. 1). The open "tracheal" channel may be used to aspirate gastric fluids with the enclosed suction catheter.

If lung inflation is unsuccessful and gastric insufflation results, the Combitube has been placed in the trachea. Ventilation is changed to the shorter "tracheal" tube (fig. 2).

A case report is presented in which a patient with neck impalement after a traffic accident was managed successfully with the Combitube.

CASE REPORT

A 33-yr-old male motorcyclist collided with the side of a truck, splintering the side panels. On arrival in the Emergency Room, it was apparent that the patient's neck had been impaled by a large wooden splinter, entering at the left angle of the mandible, traversing the pharynx and soft palate and entering in the right maxillary cavity just below the floor of the orbit.

Respiratory arrest occurred and this required immediate tracheal intubation and ventilation. The splinter partially blocked the pharynx, preventing

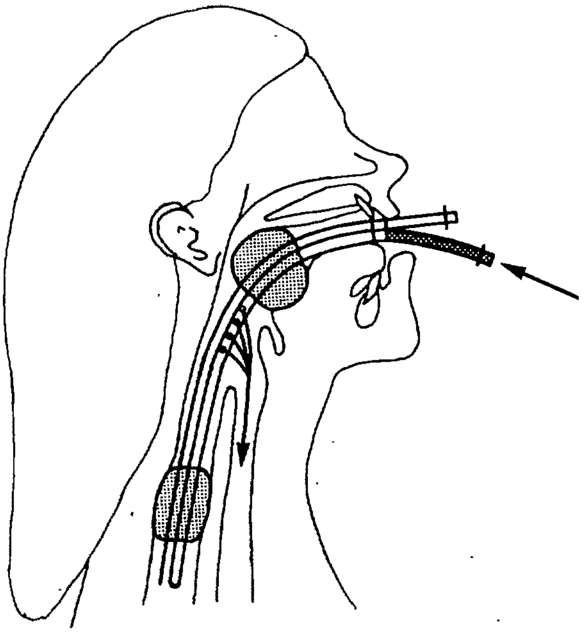

FIG. 1. The Combitube in the oesophageal position.

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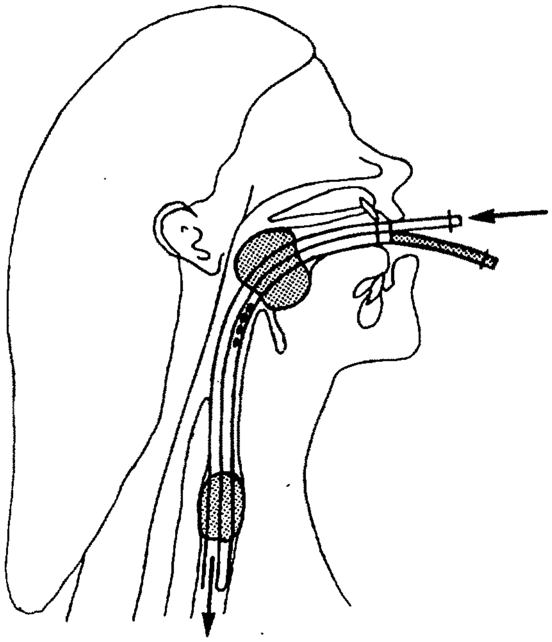

FIG. 2. The Combitube in the tracheal position.

neck movements and conventional laryngoscopy and tracheal intubation. The emergency physician introduced a Combitube, which was found to be in the trachea. Adequate ventilation and oxygenation were obtained and maintained during transportation to the hospital where tracheotomy was performed. Removal of the splinter and surgical reconstruction were then performed.

In addition to the neck impalement, the patient sustained a fractured base of skull, multiple rib fractures and a bimalleolar fracture of the left leg.

He required mechanical ventilation of the lungs for 2 weeks for a retrobulbar abscess, but was weaned successfully and discharged from hospital 2 weeks later without any neurological deficit.

DISCUSSION

The prompt establishment of a patent airway and adequate ventilation during cardiopulmonary resuscitation is essential [1]. Tracheal intubation is the preferred method for maintaining a patent airway, but the Combitube has proven to be a valuable alternative [7–9]. Previous studies have demonstrated its effectiveness in routine surgery [5, 6], cardiopulmonary resuscitation [4] and during mechanical ventilation [3].

This case report confirms that the Combitube may also have a place in the management of difficult tracheal intubation [10–12] as a non-surgical alternative. In this circumstance it has the advantage that it may be placed without laryngoscopy, and movement of the head and neck is not necessary. The oropharyngeal balloon anchors the tube and, together with the distal balloon, helps to protect the airway from blood and debris. The principal disadvantage is that the trachea cannot be aspirated when the device is placed in the oesophagus.

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APPARATUS

EFFICIENCY OF THE LEFT VENTRICLE ASSIST DEVICE HEMOPUMP IN CARDIAC FIBRILLATION

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SUMMARY

We have examined in sheep the efficiency of the Hemopump during ventricular fibrillation. Circulatory arrest was induced by electrical stimulation and maintained for 30 min. Haemodynamic measurements were recorded continuously and blood samples were taken before, during and after fibrillation to determine total body and myocardial metabolic activity. All hearts were defibrillated successfully after 30 min of fibrillation. During fibrillation, the Hemopump sustained a mean arterial pressure of about 60 mm Hg with a blood flow rate of about 2.3 litre min^{-1}. These perfusion conditions were sufficient for maintenance of aerobic myocardial metabolism, but with a borderline circulatory supply to the total organism.

KEY WORDS

Equipment: ventricular assist device (Hemopump). Heart: circulatory arrest, fibrillation.

Intra-aortic balloon counterpulsation (IABP) is the method used most frequently for mechanical circulatory support in patients with cardiogenic shock. However, the IABP is inefficient during severe cardiac arrhythmias and low arterial pressure [1]. The Hemopump is still effective if cardiac function deteriorates [2, 3], because it produces a heart action independent of blood flow from the left ventricle into the aorta [4–6]. As with the IABP, during an emergency the Hemopump may be inserted easily via the femoral artery.

The Hemopump assist device consists of a control console, an external motor and a catheter system, which contains a drive cable and a conduit for fluid which continuously flushes the system. The catheter ends in a silicone rubber inlet cannula (26 cm long, 21-French gauge) containing the axial screw (fig. 1). The screw is driven by an external magnetic motor via the drive cable. After insertion into the left ventricle, the pump system produces a maximal volume output into the aorta of 3.5 litre min^{-1} against an arterial pressure of 75 mm Hg [7].

The aim of this study was to assess the efficiency of the Hemopump in cardiac arrest during fibrillation by assessing circulation to the heart and total body.

MATERIALS AND METHODS

Studies were performed in nine sheep (mean body weight 58 (SD 11) kg, range 48–78 kg; left ventricular weight 159 (36) g). Anaesthesia was maintained with a continuous infusion of midazolam 0.25 mg kg^{-1} h^{-1} and buprenorphine 0.01 mg kg^{-1} h^{-1}. The trachea of each sheep was intubated and the lungs ventilated artificially with 70% nitrous oxide in oxygen.

Left ventricular pressure was measured by a transducer-tipped catheter and other pressures (arterial, pulmonary arterial and central venous) by strain gauge transducers. Cardiac output was esti-

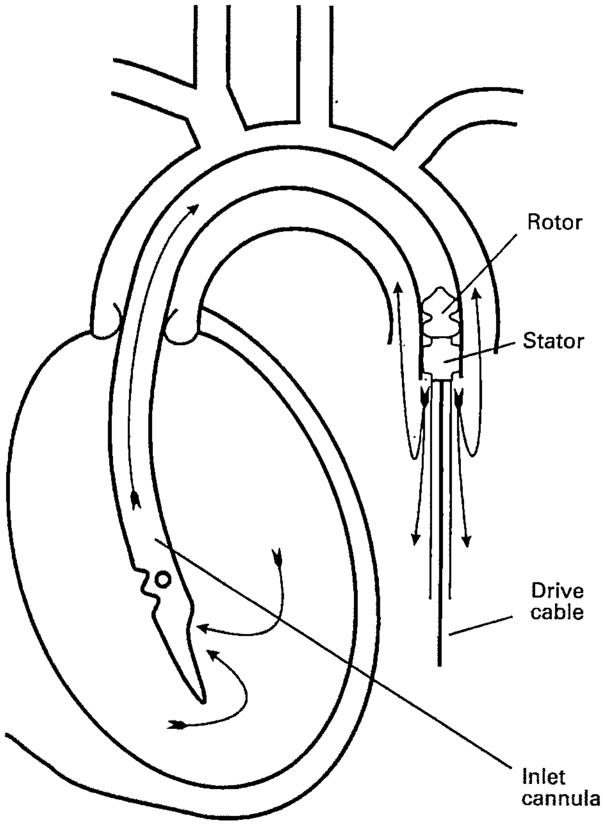

FIG. 1. Schematic diagram of the Hemopump positioned in the left ventricle.

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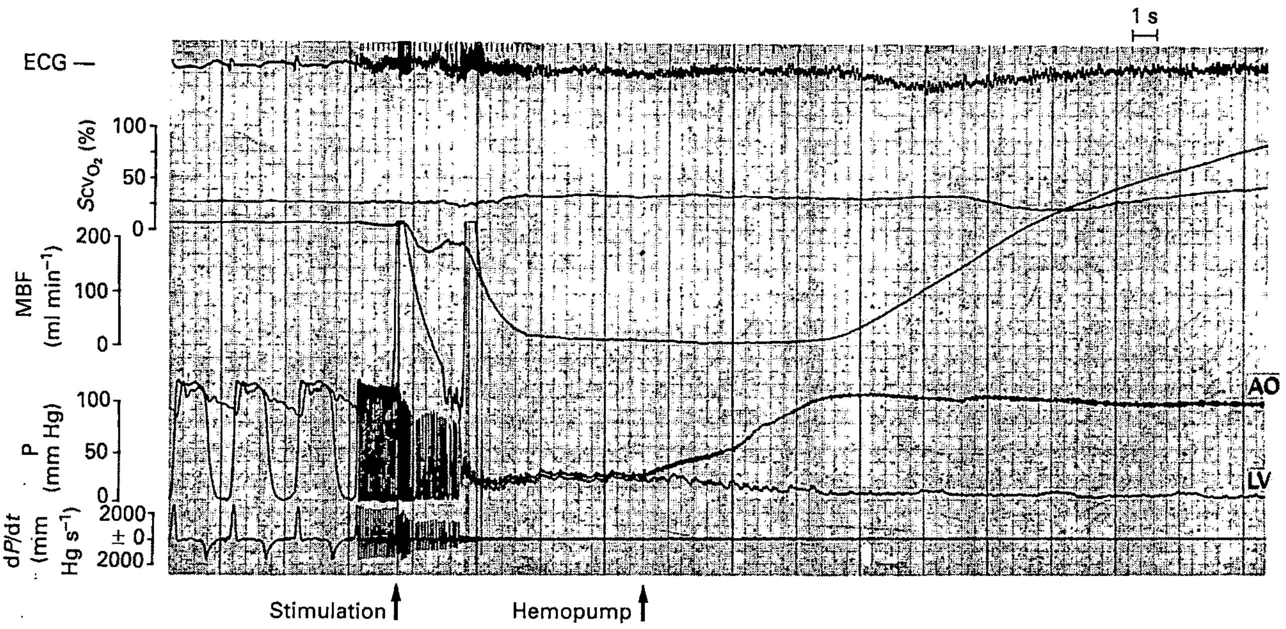

FIG. 2. Original recording during the use of the Hemopump in fibrillation induced by electrical stimulation. ECG = electrocardiogram; Scv_{O_2} = coronary venous oxygen saturation; MBF = myocardial blood flow; P = pressure (LV = left ventricular, Ao = aortic), dP/dt = rate of left ventricular pressure increase.

TABLE I. *Haemodynamic and metabolic data (mean (SD)) before, 10, 20 and 30 min during and 10 min after fibrillation. LV = Left ventricle*

		Fibrillation + Hemopump			
	Control	10 min	20 min	30 min	Sinus rhythm
Haemodynamic data					
Central venous pressure (mm Hg)	6.6 (1.9)	11.6 (2.7)	10.6 (2.5)	10.5 (2.5)	7.1 (2.6)
Pulmonary arterial pressure (mm Hg)	21 (5.6)	11.6 (3.6)	10.7 (3.0)	10.5 (2.8)	18.1 (5.5)
Mean aortic pressure (mm Hg)	96.8 (17.9)	64.0 (14.2)	60.4 (15.8)	54.6 (8.1)	72.2 (19.7)
LV end-diastolic pressure (mm Hg)	11.26 (7.61)	4.75 (7.40)	1.75 (5.88)	1.50 (5.86)	13.43 (7.79)
Hemopump flow rate (litre min^{-1})	4.7 (0.8)	2.5 (0.5)	2.4 (0.6)	2.1 (0.8)	2.4 (0.6)
Myocardial blood flow (ml min^{-1}/100 g LV)	160.1 (62.0)	108.9 (72.4)	101.2 (56.3)	97.8 (57.6)	122.1 (37.8)
Total peripheral resistance (mm Hg min ml^{-1}/kg body weight)	1.3 (0.5)	1.3 (0.4)	1.4 (0.5)	1.5 (0.5)	1.8 (0.7)
Metabolic data					
Arterial potassium content (mmol litre^{-1})	3.3 (0.3)	3.9 (0.3)	3.8 (0.3)	3.8 (0.4)	3.6 (0.4)
Myocardial potassium uptake (μmol min^{-1}/100 g LV)	−2.0 (2.0)	−15.8 (8.3)	−8.5 (10.4)	−1.8 (6.6)	−4.3 (10.9)
Arterial lactate content (mmol litre^{-1})	4.5 (1.3)	4.3 (1.0)	4.8 (1.2)	5.3 (1.6)	6.2 (1.9)
Myocardial lactate uptake (μmol min^{-1}/100 g LV)	51.3 (23)	23.5 (15.3)	29.9 (14.0)	32.9 (20.6)	38.3 (25.2)
Oxygen extraction ratio of lactate (%)	42.7 (19.26)	31.4 (31.68)	38.7 (23.72)	40.83 (27.0)	38.7 (20.7)
Coronary venous O_2 saturation (ml O_2/100 ml)	25.8 (9.6)	32.9 (14.3)	31.5 (12.6)	30.5 (12.1)	41.5 (14.2)
Total body O_2 uptake (ml O_2 min^{-1}/kg body weight)	2.6 (0.6)	2.0 (0.3)	2.1 (0.4)	1.8 (0.3)	2.0 (0.5)
Myocardial O_2 consumption (ml O_2 min^{-1}/100 g LV)	9.1 (1.7)	4.9 (1.5)	4.9 (1.2)	4.9 (1.4)	6.6 (1.8)

mated with the thermodilution technique. Measurements of serum electrolyte and lactate concentrations and oxygen content were made on pulmonary arterial, coronary venous and arterial blood samples. Myocardial blood flow (MBF) was measured using a coronary sinus flowmeter [8, 9].

The Hemopump was inserted into a large artery in the iliac region and advanced through the aorta under x-ray control until the bevelled tip of the inlet cannula was positioned within the left ventricle.

Fibrillation was induced by electrical stimulation and, after a 30-min observation period, sinus rhythm was re-established by electrical defibrillation. Haemodynamic data were recorded continuously throughout this period. Measurements of the metabolic data were carried out under baseline conditions and 10, 20 and 30 min after the onset of fibrillation and 10 min after sinus rhythm was induced.

RESULTS

Figure 2 shows a typical example of the change from normal haemodynamic state to ventricular fibrillation. At the beginning of fibrillation, a complete breakdown of circulation is evident. When the Hemopump was applied, arterial pressure increased and became distinct from the left ventricular pressure; after a delay, myocardial blood flow (MBF) increased. The lack of pulsation in the arterial pressure reflects the non-pulsatile blood flow produced by the Hemopump.

Data on the efficiency of the Hemopump are presented in table I.

After 10 min fibrillation, the blood flow supplied by the Hemopump was about 2.3 litre min^{-1}, whilst arterial pressure was maintained at about 60 mm Hg. There was a decreasing trend in both values during the period of fibrillation. Total body oxygen uptake was reduced from 2.6 to 1.9 ml min^{-1}/kg body weight at the end of fibrillation. This decrease in total body oxygen uptake was accompanied by an increase in arterial lactate concentration from 4.5 to 6.2 mmol litre^{-1}.

With the Hemopump, a steady myocardial oxygen consumption of 4.9 ml min^{-1}/100 g left ventricular weight was found during fibrillation. The baseline value of 9.1 ml min^{-1}/100 g was not reached, 10 min after restoration of sinus rhythm. One hour after the end of fibrillation, baseline values were re-established.

Potassium release from the heart was evident after 10 min of fibrillation, but not at 20 min. Concomitantly, there was a marked reduction in myocardial lactate uptake at 10 min. Thereafter, an increase in lactate uptake occurred, although baseline values were not re-established.

DISCUSSION

Compared with baseline cardiac output of 4.7 litre min^{-1}, the Hemopump produced a blood flow during fibrillation of 2.3 litre min^{-1}, with no change in peripheral resistance. Correspondingly, mean arterial pressure decreased from nearly 100 to 60 mm Hg. During fibrillation, total body oxygen uptake could not be maintained at a normal value of 2.6 ml min^{-1}/kg body weight under anaesthesia; it decreased to 2.0 ml min^{-1}/kg body weight, indicating insufficient circulatory supply to the body. As a result, arterial lactate concentration increased during the period of fibrillation. After re-establishment of normal cardiac function, a maximal lactate concentration was reflected by release of lactate from the periphery.

In spite of the inadequate total blood flow, the Hemopump maintained a normal myocardial oxygen demand of 4.9 ml min^{-1}/100 g during fibrillation [10]. Aerobic metabolism was maintained as demonstrated by the normal lactate uptake and the increasing coronary venous oxygen saturation. The ratio of lactate to myocardial oxidation metabolism also supports the view that coronary blood flow was adequate to maintain normal myocardial metabolism: the value of 40%, which changed only slightly, lay in the normal range [11]. Because of this metabolic integrity, all hearts could be defibrillated successfully. Nevertheless, total blood flow to the whole body was depressed for a short time after defibrillation and baseline conditions were not reached until 1 h later. The reason for this delayed restoration of normal pump function might be catecholamine depletion during the period of fibrillation.

We conclude that the Hemopump could provide acceptable circulatory support during a 30-min period of fibrillation, thereby preventing anaerobic myocardial metabolism, although total oxygen supply to the body was inadequate.

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British Journal of Anaesthesia 1992; **68**: 540–541

CORRESPONDENCE

CORTICOSTEROIDS AND RESISTANCE TO VECURONIUM

Sir,—In the interesting paper [1] on the possible mechanisms for resistance to vecuronium observed in patients receiving chronic treatment with corticosteroids, Parr and colleagues did not mention the steroid-induced proliferation of acetylcholine receptors (AChR) observed by Kaplan and co-workers on cultured human muscle. They reported that dexamethasone seems to act "by inducing *de novo* AChR synthesis rather than by stimulating insertion of pre-existing AChR into the plasma membrane" [2]. Another important observation is that the response to dexamethasone seems to be species-specific and is not accompanied by alterations in acetylcholinesterase activity.

These observations indicate that the quantity and quality of post-synaptic AChR could be abnormal in skeletal muscles of patients receiving chronic treatment with corticosteroids. Whether the total number of AChR or the relative preponderance of the new population of AChR is the factor to which is ascribed the resistance to vecuronium is unknown.

The second hypothesis should be favoured for the following reasons: the immature form of AChR has a reduced affinity for curare [3]; liability to hyperkalaemic accidents caused by suxamethonium is relatively poor in neurosurgical patients (without motor deficit) and seems to be absent in patients with myasthenia gravis [4] in spite of chronic treatment with large doses of corticosteroids.

F. Fiacchino
A. Giannini
Milan

1. Parr SM, Robinson BJ, Rees D, Galletly DC. Interaction between betamethasone and vecuronium. *British Journal of Anaesthesia* 1991; **67**: 447–451.
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Sir,—We acknowledge the useful comments by Drs Fiacchino and Giannini regarding the role of increased numbers of post-junctional acetylcholine receptors (AChR) in the corticosteroid-induced resistance to vecuronium. We agree that increased AChR numbers could explain, in part, the resistance to vecuronium, although we consider enhanced acetylcholine release by betamethasone is potentially the major mechanism, for the following reasons:

(1) Enhanced transmitter release reaches a plateau effect within 1 h after steroid administration [1], whereas the induction of steroid increased AChR synthesis and incorporation into the muscle cell membrane *in vitro* requires up to 24 h to develop maximal effect [2]. This immediate effect associated with enhanced transmitter release is consistent with our observations in isolated nerve–muscle preparations.

(2) Meyers [3] reported a patient receiving long-term steroid treatment who had residual paralysis after pancuronium neuromuscular block. The block was antagonized successfully within 4 min of hydrocortisone administration. The rapidity of this response also suggests an effect on neurotransmission rather than AChR numbers.

The mechanisms by which steroids antagonize neuromuscular block are likely to be multifactorial, and at present we can only speculate on the cause, based on previous scientific and clinical observations.

B. J. Robinson
D. Rees
D. C. Galletly
Wellington

1. Wilson RW, Ward MD, Johns TR. Corticosteroids: a direct effect at the neuromuscular junction. *Neurology* 1974; **24**: 1091–1095.
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PEAK SERUM BUPIVACAINE CONCENTRATION

Sir,—Dr Pihlajamäki has investigated the relationship between body weight and peak serum concentrations (*C*max) of a local analgesic agent [1]. Would one expect the relationship to be linear? If so, then the data presented predict a negative *C*max for a patient exceeding 124 kg and a *C*max for a neonate only twice that of an average adult. Clearly, as the title implies, one would expect the data to exhibit a reciprocal relationship:

$$C\mathrm{max} = \frac{K}{weight}$$

Would it not have been more appropriate, therefore, to plot $1/C\mathrm{max}$ against weight before performing least squares regression? This may have produced a better fit to the data and led to a different conclusion.

A. M. J. Atherton
Sunderland

1. Pihlajamäki KK. Inverse correlation between the peak venous serum concentration of bupivacaine and the weight of the patient during interscalene brachial plexus block. *British Journal of Anaesthesia* 1991; **67**: 621–622.

Sir,—I agree that, from my results, it is not possible to gain any information on blood concentrations in neonates or in overweight adults. However, I would doubt if results from adult patients could be extrapolated to a newborn or even a young child. In contrast, obese adult patients are not a problem, if we take the basic starting point of my study, that the authorities of many countries recommend the dose of bupivacaine to be restricted to 2 mg/kg body weight. Thus both ends of the regression line are not important.

Concerning adult patients weighing 35–100 kg (the range covered in the study), it is possible to assume a linear relation and thus to accept the method and the conclusion [1]. When plotted as Dr Atherton recommends, $1/C\mathrm{max}$ against weight, the least squares regression line is $y = 0.0073x + 0.0204$; $r = 0.4483$; $t = 2.924$; $P = 0.0061$. Thus only 20 % of the total variance could now be explained by regression ($r^2 = 0.2009$).

K. K. Pihlajamäki
Turku, Finland

1. Ingelfinger JA, Mosteller F, Thibodeau LA, Ware JH. *Biostatistics in Clinical Medicine*. New York: Macmillan Publishing Co., 1983.

IS STEROID THERAPY A CONTRAINDICATION TO EXTRADURAL ANALGESIA?

Sir,—We read with interest the important case report by Dr Sowter and colleagues [1]. They described a patient with rheumatoid arthritis receiving steroids who developed an extradural abscess 23 days after the removal of an extradural catheter and suggested that extradural analgesia should be contraindicated in patients with rheumatoid arthritis taking steroids. In our opinion such a suggestion, based on a single case, is premature.

Another report of iatrogenic extradural abscesses (which makes Dr Sowter's paper the third, and not the second, report of extradural abscesses with delayed presentation), described a woman who developed an abscess 9 days after removal of an extradural catheter. The possibility was suggested of a distant focus of infection from which bacteria could spread to the extradural space, as in the patient reported by McDonough and Cranney [2]. Dr Sowter and colleagues say only that it had not been possible for them to determine how infection developed in their patient, but it is not clear if they looked actively for a distant focus (i.e. dental caries) or if they had negative blood cultures.

Steroids are given frequently by the extradural route for the management of chronic back pain. No cases of delayed extradural abscess have been described in such patients, despite the facts that the steroid is administered directly into the extradural space and that adrenal suppression has been described up to 3 weeks after a single dose of methylprednisolone acetate 80 mg [3]. It is also common to use long-term extradural combination therapy in patients with cancer pain who are taking oral steroids. Again, there are no reports to date of extradural abscesses in this patient group.

We do not see concurrent steroid use as an absolute contraindication, but would suggest that both local steroid injection and systemic steroid therapy may increase the chance of infective complications. The crucial problem with this rare and potentially devastating complication is the delay in presentation which is a common feature of these reports. The only saving grace is the fact that pain appears to be the most consistent presenting symptom. The lesson must be that an extradural abscess should be high on the list of differential diagnoses in patients presenting with pain after extradural analgesia. We agree that steroid given by whatever route may increase the likelihood; but, because this thankfully is such a rare complication, we do not wish yet to see an absolute proscription of use of the extradural route in patients taking steroids.

H. J. McQuay
A. R. Jadad
Oxford

1. Sowter MC, Burgess NA, Woodsford PV, Lewis MH. Delayed presentation of an extradural abscess complicating thoracic extradural analgesia. *British Journal of Anaesthesia* 1992; **68**: 103–105.
2. McDonough AJ, Cranney BS. Delayed presentation of an epidural abscess. *Anaesthesia and Intensive Care* 1984; **12**: 364–366.
3. Jacobs S, Pullan PT, Potter JM, Shenfield GM. Adrenal suppression following extradural steroids. *Anaesthesia* 1983; **38**: 953–956.

Sir,—We are grateful for the opportunity to respond to the letter from McQuay and Jadad. We agree that, considering the frequent use of extradural analgesia in patients receiving steroid therapy and the use of extradural steroid injections in the management of back pain, the development of an extradural abscess is a surprisingly rare complication of this technique.

Despite a careful search for a distant focus of infection in our patient, we were unable to locate one. Our patient had no evidence of any skin, chest or urinary infection, all his teeth had been removed several years previously, blood cultures were negative and he remained afebrile throughout his postoperative course.

To regard extradural analgesia as contraindicated on the basis of one case report probably is being premature although, following our experience with this patient I think that we should be reluctant to use an extradural block in any similar patient in the future.

However, we do feel that this case has some important lessons. It demonstrates that extradural abscesses may have devastating results: they may evolve rapidly from the first symptoms of pain to irreversible neurological damage; they may present after a symptom-free interval of many days; and they may present after an apparently uneventful postoperative recovery. We agree that, when a patient complains of back pain after the use of extradural analgesia, even some time after discharge from hospital, the diagnosis of extradural abscess must be considered and urgent efforts must be made to exclude it.

M. Sowter
Glamorgan

British Journal of Anaesthesia 1992; **68**: 542

BOOK REVIEWS

Implantable Drug Delivery Systems, 1st Edn. Edited by U. Laffer, I. Bachmann-Mettler and U. Metzger. Published by Karger, Basel. Pp. 66; indexed; illustrated. Price £17.40.

A collection of essays devoted to totally implanted catheter devices will have limited appeal. This volume stresses the need to avoid complications of such catheters by suggesting that the following are necessary: (1) Use of only one type of catheter *irrespective of whether or not it is claimed to be the best, simplest or cheapest.* (2) Insertion by experienced staff. (3) Experienced nursing staff. I am happy with numbers 2 and 3, but admit to having problems with number 1. However, the fact that the book has only one advertisement (Pharmacia) may help to explain this statement.

There are eight essays with topics such as "Nursing aspects in the inpatient field" and "Nursing aspects in the outpatient field". All are related to cancer treatment and only one relates to pain therapy—a report in 117 patients. This report was published previously in *Journal of Clinical Oncology* in 1989.

The essays themselves are of equal length. The reference lists vary between 2 and 51 as the amount of data differs greatly.

It is not clear who will read this volume and find it useful, although it is meant for all medical and nursing personnel, especially those in oncology departments. It is beautifully produced, but of little or no interest to anaesthetists, intensivists, pain doctors or their supporting staff.

W. S. Nimmo

Principles and Practice of Neuroanaesthesia. By N. Edwards. Published by Chapman and Hall Medical, London. Pp. 534; indexed; illustrated. Price £45.00.

This book is unusual in that it has been written by one author, Dr Nancye Edwards, who is a Specialist Anaesthetist in Melbourne. It is a very scholarly and comprehensive review of the current art and science of neuroanaesthesia—quite a task for a single author to undertake. The advantage is that the style of writing is uniform throughout the book.

In the first five chapters, the author discusses neurophysiology, neuropathology and neuropharmacology in relation to neuroanaesthesia. Cerebral ischaemia, brain protection and induced hypotension also are considered in this introductory section. In the midst of these chapters dealing with the basic science of neuroanaesthesia is a chapter describing methods of monitoring the activity of the nervous system.

Subsequent chapters discuss the management of anaesthesia for neurosurgical conditions. Each chapter opens with a review of the particular difficulties associated with administering an anaesthetic for the surgery under discussion, describes the management of the anaesthetic and concludes with a discussion of that management when the patient is a child. The range of surgical procedures which are considered is impressive, and one chapter is devoted to the management of head injuries. The topic under consideration is discussed widely and the large number of references which are provided makes further study easy.

Unfortunately, there are one or two printing errors which should be corrected when the book goes to a second edition, and the use of different type-faces for different levels of heading could be applied more appropriately. Blood-gas tensions are given in mm Hg. The many tables and figures throughout the text are clear and are used effectively. The clinical photographs have reproduced well.

The author is to be congratulated on producing a well balanced review of neuroanaesthesia; the book will be of interest to those who are engaged in this anaesthetic sub-specialty.

J. L. Jenkinson

Pharmacokinetics for Anaesthesia, 1st Edn. By C. J. Hull. Published by Butterworth Heinemann, Oxford. Pp. 421; indexed; illustrated. Price £60.00.

Anaesthetists ignore a basic knowledge of pharmacokinetics at their peril. However, in common with religion, the subject attracts its share of fanatics as well as more enlightened believers. Knowledge with understanding has too often been shrouded in mystery, confusion and unsubstantiated doctrine. Enlightenment in the form of a single text is now available and this offering by Professor Hull is the best explanation of the principles and practice of pharmacokinetics applied to anaesthesia.

Dr Papper, in his foreward, describes the book as a very large if not monumental task in gathering together the material. The text itself is in five sections: Basic essentials; What happens to drugs in the body; Pharmacokinetic analysis; Pharmacokinetics of some drugs used in anaesthesia; Putting pharmacokinetics to work. There are also appendices to calculate area-under-the-curve and to describe the computer program which may be purchased to accompany the book.

The basic essentials section contains four chapters describing mathematical functions, molecules, passage across membranes and some basic pharmacokinetic concepts. These will be good revision for most readers, but the mathematics might be daunting for some.

Section 2 deals with drug absorption, distribution, excretion, pharmacodynamics and the effects of age and other factors on drug disposition. The amount of text devoted to each subject varies greatly and my personal emphasis would have been different. For example, only half a page is devoted to i.m. and s.c. administration; this could have been greater, with some interesting examples taken from anaesthetic practice. Only one page of text devoted to extradural administration is also disappointing.

Sections 3 and 4 are the strong points of the book with clear, useful teaching and many examples. In particular, I enjoyed the section on pharmacokinetics of drugs used in anaesthesia—the book is worth buying for this section alone. It is well referenced, comprehensive and accurate, with many figures from learned journals. These chapters will be invaluable to every anaesthetist and would make an excellent stand-alone text. My concern that they will not be updated often enough because they are found in such a large book could be lessened if they were available separately.

"Putting Pharmacokinetics to Work" is too complicated, in my view. A simpler approach to designing dosage regimens and their assessment would have been more valuable to the reader who had not read his way through the previous 376 pages but wanted to dip into this interesting and relevant topic. This is really a criticism of the reader rather than the book, but it highlights what I believe to be the only flaw with this excellent work.

No one can deny the importance of pharmacokinetic knowledge in the safe and effective use of anaesthetic drugs. It is undeniable that this work is the best comprehensive attempt to educate, remind and inform practitioners of useful information. It does not really fill a gap on many bookshelves, because not many knew there was a gap. In common with *The Bible*, it is great, but not enough people who would benefit will read it. That is a pity.

W. S. Nimmo

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"*I would have everie man write what he knowes and no more.*"—MONTAIGNE

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EDITORIAL

NEUROMUSCULAR BLOCKING DRUGS AND RENAL FAILURE

In patients who have impaired renal function, the use of many drugs poses problems in view of the reliance of most drugs on the kidney for final elimination. The neuromuscular blocking agents are no exception; all are ionized, water-soluble compounds and, as a result, would be expected to be filtered freely at the glomerulus and not to be reabsorbed. Thus one might expect them to rely principally upon intact renal function for termination of effect. Only the free molecules are filtered, not those bound to plasma proteins. However, the neuromuscular blocking drugs are not greatly bound to plasma proteins (up to about 50%) [1], and the rate of equilibration between bound and unbound forms is very rapid; it is unlikely, therefore, that plasma protein binding, or any changes in this binding, have any significant effect on the renal excretion of the neuromuscular blocking agents.

If many of the older established texts in the specialty are consulted, it may be seen that caution was advised in all cases when using a neuromuscular blocking agent in a patient with impaired renal function. The principal reason advanced was the risk of postoperative "recurarization". The problem, as it was perceived at the time, was that the elimination of the neuromuscular blocking agent was considerably reduced in renal failure, to the extent that its action was extended significantly into the postoperative period. The argument then continued to suggest that as the effect of the antagonist began to wane there would be a reappearance of neuromuscular block [2]. Subsequent evidence has cast doubt on this reasoning by demonstrating that the anticholinesterases also rely upon the kidney to some extent for elimination, and that their duration of action is prolonged also in renal failure [3–5]. Nevertheless, difficulties or delays in antagonism of block, or postoperative weakness occurred.

While it is true that the neuromuscular blocking agents are excreted renally, the kidney is not, of course, the only pathway for removal of active molecules from blood (and hence, by implication, from their site of action, the "active biophase"). Redistribution plays an important role in the reduction of plasma concentrations, particularly in the early phase after administration of a bolus dose of the agent. Alternative routes of elimination exist for many of the agents, including in particular, hepatic metabolism and biliary excretion. All the neuromuscular blocking agents are subject, to a greater or lesser degree, to metabolic or degradative processes which result ultimately in a molecule which is pharmacologically inactive.

The agent which comes foremost into every anaesthetist's mind with respect to prolongation of action in renal failure is gallamine. The principal reason for this is that gallamine is metabolized to such a small extent that it relies almost solely on the kidney for elimination and therefore for termination of effect [6]. Theoretically, its action would be prolonged almost infinitely in patients with absent renal function, although in practice an approximately six-fold increase in terminal half-life has been reported [7]. Gallamine is generally regarded as being contraindicated in patients with impaired renal function.

The other long established neuromuscular blocking agents are affected to a lesser extent. The plasma clearance of pancuronium is decreased approximately 33% [8] to 50% [9] of that of normal patients in the presence of renal failure. The elimination half-life of tubocurarine has been reported to be increased from 232 min in normal patients to 330 min in renal failure patients [10]. Alcuronium is also eliminated more slowly in patients with impaired renal function [11–13]. None of these neuromuscular blocking agents would seem, therefore, to be ideal for use in patients with impaired renal function.

It is not only the elimination characteristics of a drug which dictate its usefulness in renal failure, but also many of its additional effects. Renal failure patients commonly have a number of other disease processes which might result from, or be the causative factor of, the renal failure. It is important, therefore, to choose a drug with as few undesirable side effects as possible.

In the early 1980s, two new intermediate-acting, non-depolarizing neuromuscular blocking agents, atracurium and vecuronium, were introduced, and it rapidly became apparent that both were superior to any of the previously available neuromuscular blocking agents for use in renal failure.

Atracurium has one notable advantage which sets it apart from all the other neuromuscular blocking agents, namely that it is spontaneously degraded in the body to metabolites which are devoid of neuromuscular blocking activity. There is one metabolite, laudanosine, which may produce cerebral excitation in laboratory animals. Because laudanosine is renally excreted, this metabolite, but not its parent drug, accumulates and much debate has centred around the possibility of significant adverse effects which might result from accumulation of laudanosine in renal failure. This debate is not yet concluded. The pharmacokinetics of atracurium are nevertheless unaffected by renal failure [14] and a dose of atracurium has the same duration of action in a renal failure patient as in a normal patient [14].

Vecuronium is excreted renally, but also metabolized fairly rapidly. It is also taken up in various tissues of the body and has a large volume of distribution. Although the effect of renal failure on vecuronium is small, there is a gradual increase in duration of action with repeated doses, and this cumulation is presumed to be a result of gradual saturation of peripheral storage sites [15]. There is now no doubt that prolonged neuromuscular block may result from the use of an infusion or from larger doses of vecuronium in patients with severely impaired renal function [16, 17]. Indeed, it is possible to demonstrate a slight, yet significant increase in duration of action after a single dose in renal failure patients [18]. The possibility has been raised that it is accumulation of the 3-desacetyl metabolite more than the parent compound which contributes to this effect [16].

There are several new drugs undergoing assessment. Mivacurium represents a significant advance in that it has a shorter duration of effect than either atracurium or vecuronium [19, 20]. This should make it of significant value for short surgical cases. Its action may be sufficiently brief that potentially it does not require antagonism. Mivacurium, in common with atracurium and vecuronium, has minimal cardiovascular side effects [21]. On these counts, it would seem to be of potential value in the renal patient. Mivacurium is metabolized by plasma cholinesterase [22] (not acetylcholinesterase) to substances which are devoid of neuromuscular action, and does not rely upon renal excretion for its inactivation. It is interesting to note that the rate of hydrolysis by plasma cholinesterase (which is in excess) depends upon the concentration of mivacurium in the plasma. Thus the greater the concentration of mivacurium, the more rapid its breakdown and, unlike the case with other neuromuscular blocking agents, increasing the dose has only a small effect upon the duration of action. Clearly, the breakdown of mivacurium would be affected by any factor which interferes with either the activity or the quantity of plasma cholinesterase (e.g. anticholinesterases). The destruction of mivacurium is reduced also (hence its duration of action is increased) in patients with atypical plasma cholinesterase [23]. Thus one might expect it not to be affected by renal impairment.

Phillips and Hunter, in the May issue of this Journal [24], described a comparison of the characteristics of mivacurium in patients with no renal function with those of normal patients. They showed that the action of mivacurium was prolonged in the anephric patient, but not to any great extent. They suggested that there was probably no change in elimination directly as a result of the renal failure, but that there was a decrease in plasma cholinesterase activity, which is a common finding in renal failure. It would appear, therefore, that mivacurium is safe to use in renal failure patients, although a small prolongation of effect should be expected.

A further observation was also made by Phillips and Hunter [24]. They noted that the use of an anticholinesterase accelerated the recovery of a mivacurium neuromuscular block by only a small amount. Administration of an anticholinesterase inhibits plasma cholinesterase in addition to acetylcholinesterase. It is likely, therefore, that the rate of destruction of mivacurium is reduced at the same time as pharmacological reversal progresses at the neuromuscular junction. It may transpire when mivacurium is in clinical use, therefore, that it is preferable to avoid anticholinesterases when antagonizing neuromuscular block.

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ORIGINAL ARTICLES

A NEW FOUR-PARAMETER THRESHOLD MODEL FOR THE PLASMA ATRACURIUM CONCENTRATION–RESPONSE RELATIONSHIP

C. J. R. PARKER AND J. M. HUNTER

SUMMARY

The plasma concentration of atracurium and the electromyographic depression of the first response of the train-of-four (T1:T0) were measured during and after recovery from a 10-min infusion of atracurium 0.25 mg kg^{-1} in 14 patients anaesthetized with 66% nitrous oxide and 0.9% isoflurane (end-tidal) in oxygen. A standard pharmacodynamic model was fitted to the data; a small but consistent discrepancy was found between the time and rate of onset of depression of the ratio T1:T0 and the predictions of the standard biophase model of best fit to the data. This discrepancy is reduced by the inclusion of a threshold term ($C_P{}^{ss}{}_\theta$) in the model to represent the greatest steady state plasma concentration which would just fail to evoke an effect. The values of $C_P{}^{ss}{}_\theta$ correlated significantly with the values of $C_P{}^{ss}{}_{50}$ ($r = +0.627$; $P < 0.02$). The estimates of $C_P{}^{ss}{}_{50}$ and k_{eo} from the two models are very similar; the estimate of Γ, the slope of the concentration–response curve, was less in the threshold model. The relationship of the present threshold model to existing knowledge of neuromuscular physiology is discussed.

KEY WORDS

Neuromuscular relaxants: atracurium. Neuromuscular transmission: train-of-four response. Pharmacodynamics: model.

Early attempts to relate the action of the non-depolarizing neuromuscular blocking drugs to their plasma concentration were frustrated by the fact that the relationship differs during onset and recovery; a given degree of twitch depression during onset is associated with a greater plasma drug concentration than that during recovery [1]. This discrepancy, which reflects the fact that the site of action is peripheral to the plasma, was overcome by the application of an effect compartment model by Hull and colleagues [2], and Sheiner and colleagues [3]. This model is characterized by three parameters: two define the position and slope of the concentration–response relationship at the site of action, generally denoted $C_P{}^{ss}{}_{50}$ and Γ, respectively; the third parameter defines the rate of equilibration of drug in the plasma with the site of action, and is denoted k_{eo}, the rate constant for exit of drug from the effect compartment.

The model has been applied widely to the non-depolarizing neuromuscular blocking drugs including atracurium [4–7], for which there arises the additional complication of possible degradation of drug close to its site of action, in addition to its return to the plasma. A similar scheme has been envisaged for other classes of drug, including the opioids [8] and propofol [9].

Despite the power and wide application of the model it remains a means whereby data obtained during the onset and recovery of drug action may be superimposed; it is not a summary of available knowledge of the neuromuscular junction. Furthermore, whereas Sheiner and colleagues offered a partial validation of the model by comparing the quality of its fit to the data with that of more restricted models [3], subsequent workers have not envisaged further alteration to the structure of the model.

We report a small but systematic discrepancy between the observed time and rate of onset of the action of atracurium and the predictions of the standard model of best fit to the data as a whole. We have shown that the discrepancy was greatly ameliorated by inclusion of a threshold in the effect compartment. The relationship of this modification of the model to the existing knowledge concerning the margin of safety of neuromuscular function is discussed. A preliminary report of this work has been presented elsewhere [10].

PATIENTS AND METHODS

We studied 14 healthy patients undergoing elective minor surgery requiring the use of neuromuscular block. The study was approved by the Ethics Committee of the Royal Liverpool Hospital and informed consent was obtained.

Premedication consisted of either promethazine 50 mg or diazepam 10 mg, orally on the night before surgery, or cyclizine 37.5–50 mg with morphine 7.5–10 mg i.m. 1 h before surgery. In those patients admitted to hospital on the day of surgery, premedication was omitted.

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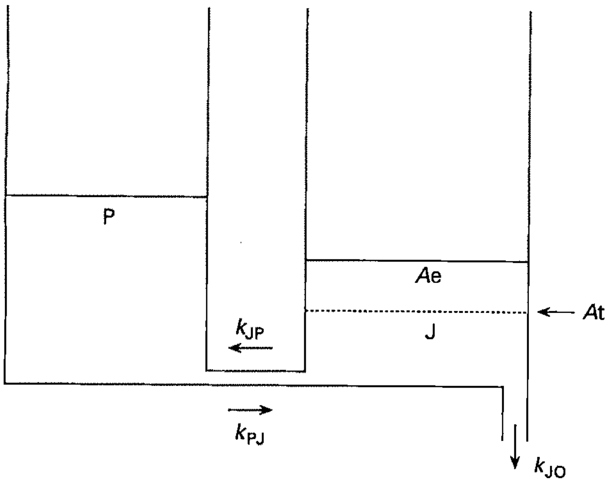

FIG. 1. The threshold pharmacodynamic model. The plasma compartment, denoted P, is connected to the site of action, compartment J, by a pathway in which drug moves at rates determined by rate constants k_{JP} and k_{PJ}. Drug may leave compartment J without returning to the plasma at a rate determined by k_{JO}. The magnitude of drug effect is related to the amount of drug, *A*e, greater than threshold in compartment J.

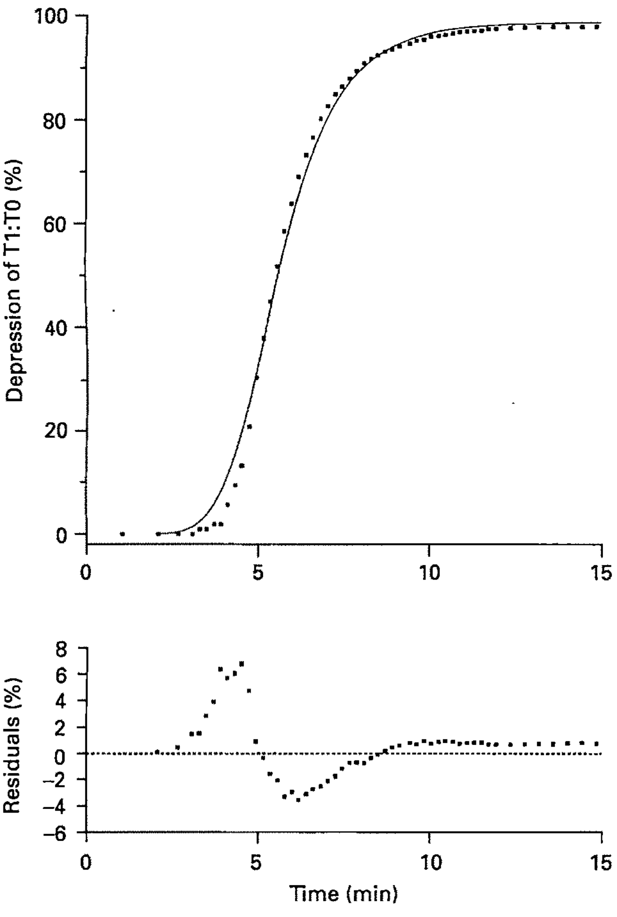

FIG. 2. Discrepancy between the measured onset of depression of T1:T0 (■) and the prediction of the standard, three parameter, biophase model (——) (upper graph) for patient No. 8, and residual errors plotted on an enlarged scale (lower graph).

Anaesthesia was induced with fentanyl 50–200 µg and thiopentone 250–500 mg and maintained with 0.9% isoflurane (end-tidal) and 66% nitrous oxide in oxygen. The end-tidal concentration of isoflurane was monitored using an infra-red analyser (Datex "Normac"). After induction of anaesthesia, electromyographic monitoring of the height of the surface compound action potential of the adductor pollicis of one hand in response to trains of four supramaximal stimuli to the ulnar nerve was commenced using the Medelec MS6 [11]. Recording of the electromyographic effect during profound block was facilitated by the fact that the amplifier gain could be altered according to signal size. In general, the height of the evoked electromyographic effect was quantified with a random error of not more than 1%.

A vein in the antecubital fossa of the arm used for electromyographic monitoring was cannulated for blood sampling. A vein in the opposite forearm was cannulated for administration of atracurium.

After 20 min, atracurium 0.25 mg kg^{-1} was given by constant rate infusion over a period of 10 min. Ventilation was controlled and the trachea intubated when appropriate; end-tidal carbon dioxide tension was maintained in the range 4.0–5.3 kPa (Datex "Capnomac").

Pharmacological antagonism of neuromuscular block was not used; neuromuscular monitoring was continued until both the ratios T1:T0 and T4:T1 were 80% or greater (in one patient monitoring was discontinued when T1:T0 recovered to 78.5%). After recovery from neuromuscular block and the end of surgery, anaesthesia was discontinued, spontaneous ventilation re-established and the trachea extubated.

Heparinized blood samples (2.5 ml) were taken before and at 1, 2, 4, 6, 8 and 10 min after the start of the infusion, and at 1, 2, 4, 6, 8, 10, 15, 20, 25, 30, 40, 50, 60, 75 and 90 min after the end of the infusion. The samples were immediately acidified and cooled, and plasma was separated promptly. The plasma was frozen rapidly in liquid nitrogen and stored at −20 °C until subsequent analysis of the atracurium concentration as described previously [11].

Data analysis

The threshold pharmacodynamic model is illustrated in figure 1 and described in the Appendix. It is defined by four parameters: three are directly comparable to those of the standard model ($C_P{}^{ss}{}_{50}$, Γ, k_{eo}). The fourth parameter, $C_P{}^{ss}{}_{\Theta}$, is the steady state plasma concentration of atracurium which would just fail to evoke an effect.

For each patient, the standard and threshold pharmacodynamic models were fitted to the data for depression of the ratio T1:T0. A specific compartmental model of disposition was abandoned in favour of using numerical methods to define terms which relate the effect compartment concentration to the plasma concentration as measured (see Appendix). This freed the pharmacodynamic model from any potential mis-specification inherent in a compartmental pharmacokinetic model. The Gauss–Newton algorithm was used to find the least squares fit of the model to the data. No attempt was made to weight the data points.

The closeness of fit of the data and the model predictions were examined by consideration of residual error. The total sum of squared residual errors was calculated; formal comparison of the residual errors in the two models was not undertaken using the *F* test because the data formed a time series, and so successive residual errors were correlated. Residual error was examined using residual plots, and by calculation of the Durbin–Watson statistic [12], which evaluates the serial correlation of residual errors. The discrepancy between the model predictions and the data was examined further by comparison of the measured and predicted values of the time to 10% depression of T1:T0 and the change in T1:T0 which occurred during the 1 min thereafter.

RESULTS

Seven patients were male and seven were female; mean age was 36.4 (SD 15.8) yr (range 19–65 yr); mean weight was 63 (11.3) kg (range 48–89 kg).

The pharmacokinetic profile of these patients has been illustrated previously [11].

An example of the measured depression of T1:T0 during the first 15 min after the start of the atracurium infusion for patient No. 8, and the predictions of the standard model of best fit are shown in figure 2, together with the residual errors. The depression of T1:T0 began later, but then proceeded more rapidly than the depression predicted by the standard model of best fit. This discrepancy is reflected in the pattern of residual errors. The figure is entirely typical; a similar pattern of residual errors was found for all the patients studied.

The magnitude of residual error for the fit of both models to the data of each patient is shown in table I. It may be seen that the threshold term reduced the residual error in each patient, in many instances substantially.

The degree of correlation of the residual errors, defined by the Durbin–Watson statistic also is shown for each patient in table I. In every patient, the serial correlation of residual errors was reduced by inclusion of the threshold term.

The time to 10% depression of T1:T0 predicted by both the standard and threshold models is plotted against the measured time in figure 3. It can be seen that, whereas the standard model underestimated the time to 10% depression in every case (by between 0.14 and 0.47 min), the threshold model made a more accurate prediction.

The standard model also underestimated the change during the 1 min after 10% depression in all

TABLE I. *Number of electromyographic data points (d.p.) used to fit the model and total sum of squared residual errors (SSE), for each patient, for both the standard and threshold models. The sum of squared residual errors has been multiplied by 10^2 for convenience of presentation; thus, for example, the sum of squared residual errors for patient No. 1 with the standard model is actually 0.0334. The Durbin–Watson statistic also is shown for each patient for both the standard and threshold models. (If there is no serial correlation of residual errors, then the Durbin–Watson statistic is 2. A positive serial autocorrelation is indicated by a decrease in the value toward 0.)*

		SSE ($\times 10^2$)		Durbin–Watson statistic	
Patient No.	No. of d.p.	Standard model	Threshold model	Standard model	Threshold model
1	129	3.34	0.60	0.111	0.390
2	110	2.35	0.80	0.187	0.478
3	109	1.55	0.60	0.266	0.554
4	113	4.59	0.81	0.082	0.251
5	106	6.25	2.15	0.062	0.149
6	96	4.21	2.87	0.069	0.112
7	90	5.65	1.92	0.106	0.225
8	134	4.39	0.58	0.092	0.334
9	118	5.74	0.67	0.138	0.204
10	120	7.87	3.19	0.083	0.180
11	114	7.63	2.65	0.067	0.114
12	126	4.90	1.17	0.113	0.208
13	110	4.59	1.16	0.104	0.280
14	110	2.85	1.09	0.114	0.265

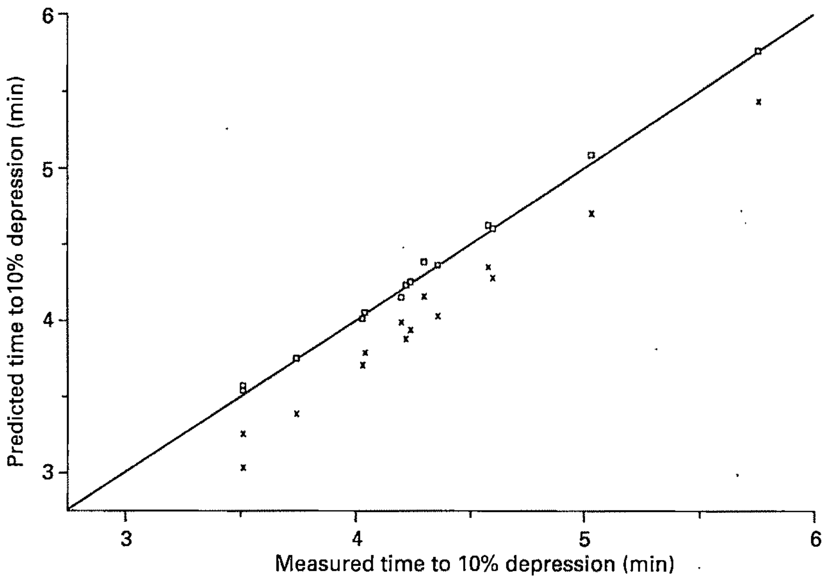

FIG. 3. Predicted time to 10% depression of T1:T0 plotted against measured time, in each patient, for both the standard (×) and threshold (□) pharmacodynamic models, together with the line of identity (——). The standard model consistently underestimates the time to 10% depression; the threshold model gives a better prediction in every patient.

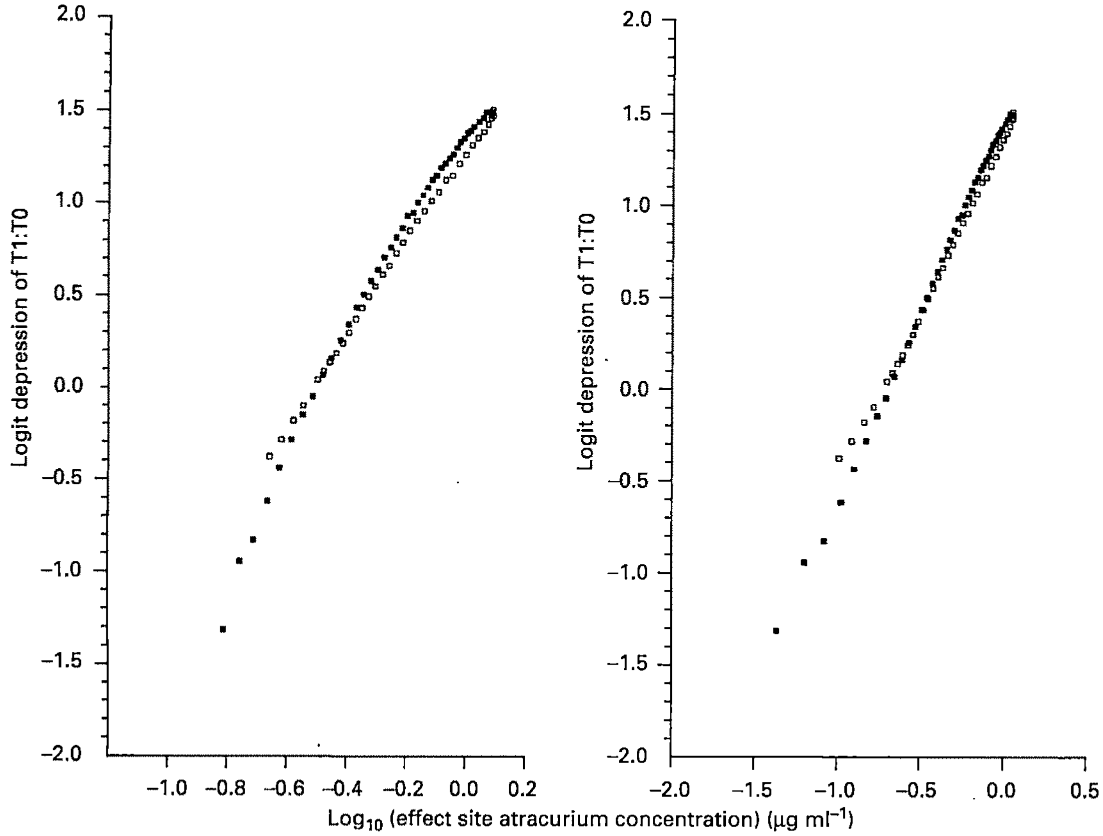

FIG. 4. Logit of depression of T1 : T0 plotted against effect site concentration (on a logarithmic scale) for the standard model (left) and threshold model (right) for patient No. 1; the figure is typical of the results for all of the patients. With the standard model, the relationship during onset (■) departs from linearity; the lower points (obtained during the earliest phase of onset) are shifted to the right relative to a straight line through the data. This discrepancy is reduced with the threshold model. □ = Recovery.

TABLE II. *Values of the parameters for both the standard and threshold pharmacodynamic models (mean (SD))*

	Standard model	Threshold model
$C_P{}^{ss}{}_{50}$ (ng ml^{-1})	359 (65)	357 (65)
k_{eo} (min^{-1})	0.117 (0.024)	0.119 (0.025)
Γ	3.91 (0.57)	2.38 (0.31)
$C_P{}^{ss}{}_{\Theta}$ (ng ml^{-1})	—	159 (40)

14 patients (by from 2.6 to 14.4%). Although the threshold model overestimated the value in all but two of the patients, the absolute error was less than for the standard model in 11 of the 14 patients.

The logit depression of T1 : T0 for patient No. 1 is plotted against the effect site concentration for the standard model in figure 4, which is typical of results from all patients studied. Whilst there was close approximation of data from onset and recovery, the relationship during onset was not linear; points during the early phase of onset were displaced to the right. This feature is inconsistent with the application of a logistic concentration–response relationship within the effect site of the standard model. The inclusion of a threshold at the effect site ameliorated the discrepancy.

The fitted values of the parameters are summarized in table II for both the standard and threshold models. The values of $C_P{}^{ss}{}_{50}$ and k_{eo} were altered little by the choice of model; in no patient was $C_P{}^{ss}{}_{50}$ different by more than 1.5% between the two models, and for k_{eo} the difference was in no case greater than 4% of the parameter value. The fitted values of Γ were substantially different between the two models; in every case the value of Γ was less in the threshold model than in the standard model.

The fitted values of the parameter $C_P{}^{ss}{}_{\Theta}$ range from 81.8 to 225.1 ng ml^{-1}. In every case a positive value was obtained. The values of $C_P{}^{ss}{}_{\Theta}$ correlated positively with the values of $C_P{}^{ss}{}_{50}$ in the same patient ($r = +0.627$; 12 d.f.; $P < 0.02$).

DISCUSSION

The effect compartment model was applied to the analysis of the effects of the non-depolarizing neuromuscular blocking drugs more than a decade ago [2, 3], and it is still used widely [6, 7]. It explicitly separates factors which affect disposition from those which affect drug response at the site of action, and it enables a maximum of information to be obtained from the study of each patient. The modification of this successful model should therefore not be undertaken without good reason, and the justification should proceed on both statistical and conceptual grounds. Furthermore, modifications should be parsimonious—that is, a small modification should be expected to produce a substantial enhancement of the explanatory power.

The statistical justification of the inclusion of the threshold parameter in the model is complicated by the fact that the electromyographic data set comprises many closely spaced observations; each observation is similar to the preceding one. The residual errors from the fit of the (deterministic) model also form a time series with considerable serial correlation. This is borne out by the values of the Durbin–Watson statistic (table I). Thus an assumption of the F test is violated and the test is not applicable. The problem is not that the F test does not find a "statistically significant" reduction in residual error, but that the significance is absurdly overstated, by a factor related to the correlation of the residual errors. This is illustrated by the results for patient No. 1, for whom $F_{1,129} = 587.5$.

The F test was used by Sheiner and colleagues [3] to compare the standard model with more restricted variants, and very highly significant values of F were obtained. Because the statistical justification of the threshold model eludes a single test, reliance must be placed on other arguments.

First, an adequate model should reproduce accurately the pattern of the results, apart from random errors. In respect of the time and rate of onset of depression of T1:T0, it is clear both that the standard model fails to do so and that the threshold model represents a substantial improvement.

Second, the sign of the threshold parameter $C_{P}^{ss}{}_{\theta}$ gives evidence for its justification; thus if $C_{P}^{ss}{}_{\theta}$ were redundant, its fitted value should be close to zero, and its sign might be positive in some subjects and negative in others. In fact, the fitted value of $C_{P}^{ss}{}_{\theta}$ was positive in all 14 subjects; this provides robust evidence that the threshold parameter is not redundant.

Third, the serial autocorrelation of residual errors is reduced in every patient by incorporation of the threshold parameter. This autocorrelation reflects the preponderance of systematic over random errors in the fit of the model to the data, and it is clear, therefore, that the systematic error in the model is reduced by the inclusion of the threshold term.

The formulation of an effect compartment model requires the synchronization of two separate data sets (for plasma concentration and electromyographic effect), and the question arises as to whether or not the error of the standard model in estimating the time to 10% depression of T1:T0 might be an artefact arising from errors in the timing of the data points. Whilst the time of the electromyographic data points is known to within 1–2 s, the timing of the blood samples is inevitably subject to greater errors. The design of this study included two factors which militated against the overstatement of the need to postulate a threshold. First, the use of venous rather than arterial blood samples, whilst giving a less accurate picture of the plasma concentration to which the arterial end of the muscle capillary is exposed, leads to the inclusion of a time delay in the plasma concentration data in the direction of underestimating the exposure of the muscle to drug during the early minutes of its administration. Second, the abandonment of a compartmental pharmacokinetic model in favour of fitting the dynamic model to the plasma concentration profile *as measured* avoids the possibility of a gross overestimate of the drug concentration to which the site of action is exposed during the early minutes of onset. Circulatory delays have been preserved in the data set used to fit the present models, and the drug concentration in the plasma close to the site of action has been estimated more accurately than it would have been by the concentration in the central compartment of a pharmacokinetic model (see Appendix).

The inclusion of the threshold term is robustly supported by the findings with respect to the change in block during the 1 min after the onset of 10% depression. This represents a *rate of change* of effect and is thus more immune to discrepancies in the synchronization of the data sets than is a single estimate of time.

Changes in the concentration of isoflurane at the neuromuscular junction during the onset of block might, conceivably, account for some of the discrepancy between the present findings and the predictions of the standard model. Whilst equilibration of isoflurane with the muscle was incomplete when the atracurium infusion was started [13], it is difficult to envisage that the concentration of isoflurane in the muscle could be changing sufficiently rapidly to affect the rate of onset of block as consistently as was found. Furthermore, a similar discrepancy has been noted in patients anaesthetized without the use of a volatile anaesthetic agent, some of the results from whom have been reported in preliminary form [14].

The discrepancy between the predicted and measured rate and time of onset of a non-depolarizing neuromuscular blocking drug noted in the present report may be discerned retrospectively in previous work. Thus measured and predicted effects have been plotted for a single individual given tubocurarine [15] for whom, upon close examination of figure 2, a discrepancy very similar to that noted here may be seen.

Whilst the concept of a threshold in the study of pharmacological effects was identified more than two decades ago [16], the presently postulated threshold term is also consistent with much evidence on the physiology of the neuromuscular junction. As early as 1956, the size of the normal end-plate potential was estimated to be about 45 mV [17], some three times greater than the threshold for initiation of an action potential. Thus there exists a margin of safety in the relative size of the end-plate potential and that needed to excite the muscle.

Knowledge of the margin of safety of neuromuscular transmission was advanced in 1967 by Paton and Waud [18]. They compared the doses of a non-depolarizing neuromuscular blocking drug required to block the effects of a humoral agonist injected intra-arterially, with the effect of neural stimulation. The response to neural stimulation was unaltered until about 76% of the postjunctional receptors were blocked.

The values of the threshold parameter, $C_{P}^{ss}{}_{\theta}$, correlated with the values of $C_{P}^{ss}{}_{50}$ in the same subject, and the ratio $C_{P}^{ss}{}_{\theta}:C_{P}^{ss}{}_{50}$ was about 40%. The magnitude of the margin of safety defined by Paton and Waud [18] might lead one to expect a somewhat greater value. The present model identifies the site of action as a single compartment, however, and the parameter $C_P^{ss}{}_\theta$ is defined as that value of plasma concentration which just fails to evoke any depression of T1:T0. Thus $C_P^{ss}{}_\theta$ is the margin of safety of the most sensitive end-plates, rather than the margin of safety of the muscle as a whole. The heterogeneity of the muscle militates against finding a greater value of $C_P^{ss}{}_\theta$.

The present model, the first explicit demonstration of a margin of safety of neuromuscular transmission in the human, sheds light on an important clinical problem: the time to onset of action of the non-depolarizing neuromuscular blocking drugs. The existence of a threshold suggests that it may not be possible to achieve rapid onset of block with a non-depolarizing neuromuscular blocking drug.

APPENDIX

The equations which define the behaviour of the threshold model are derived below, in a manner similar to that given by Sheiner and others [3].

The threshold model is illustrated in figure 1. The observed effect on neuromuscular function is considered to be related to the amount of drug greater than the threshold concentration in compartment J, which is considered to be sufficiently small that the disposition of drug there has a negligible effect on the amount of drug in compartment P. The following definitions are given:

A_J = amount of drug in compartment J
Ae = amount by which the amount of drug in compartment J exceeds the threshold
At = amount of drug in compartment J when the concentration there is at the threshold
A_P = amount of drug in (plasma) compartment P
C_P = drug concentration in the plasma compartment
V_P = volume of the plasma compartment
k_{PJ}, k_{JP}, k_{JO} = rate constants assigned in figure 1
Initial values are designated with superscript o, for example A_J^{o}
Laplace transforms are designated with a bar, for example $\bar{A}_P$
The Laplacian operator is designated s.

Thus

$$\begin{bmatrix} Ae = A_J - At & \text{if } A_J > At \\ Ae = 0 & \text{otherwise.} \end{bmatrix}$$

Considering entry and exit of drug to and from compartment J, we can write:

$$\frac{dA_J}{dt} = A_P k_{PJ} - A_J(k_{JP} + k_{JO})$$

Taking the Laplace transform of this equation and rearranging, we have:

$$\bar{A}_J(s + k_{JP} + k_{JO}) = \bar{A}_P k_{PJ} + A_J^{o}$$

Initially: $t = 0$, $A_J^{o} = 0$.

We denote the sum of rate constants for drug exit from compartment J by k_{eo}. That is:

$$k_{eo} = k_{JP} + k_{JO}$$

Thus:

$$\bar{A}_J = \frac{\bar{A}_P k_{PJ}}{s + k_{eo}}$$

To obtain the inverse transform of $\bar{A}_J$ requires application of the convolution theorem. Thus an expression for A_J at any time, t, may be written in terms of the time course of A_P and the model parameters k_{eo} and k_{PJ}.

The amount of drug in compartment J at any time (t) may be written:

$$A_J(t) = k_{PJ} \int_0^t A_P(T)\, e^{-k_{eo}(t-T)}\, dT$$

so:

$$A_J(t) = k_{PJ} V_P e^{-k_{eo}t} \int_0^t C_P(T)\, e^{k_{eo}T}\, dT \qquad (1)$$

As noted above, the effect on neuromuscular function (E) is considered to be exerted by the drug in compartment J which is in excess of the threshold, Ae. An equation of the form used previously [3] is proposed:

$$\begin{bmatrix} E = \dfrac{Ae^{\Gamma}}{Ae^{\Gamma} + Ae_{50}{}^{\Gamma}} & \text{if } A_J > At & (2) \\ E = 0 & \text{otherwise} & (2) \end{bmatrix}$$

where: E = observed effect on neuromuscular function; Γ = slope of the relation between logit E and log Ae; Ae_{50} is the value of Ae when the effect is half maximal.

For any value of A_J there is a value of C_P which would produce that value of A_J at steady state [3]. This value is denoted C_P^{ss}. We may designate:

$C_P^{ss}{}_{50}$ is the value of C_P which, if maintained at steady state, will produce a half maximal effect.
$C_P^{ss}{}_\theta$ is the value of C_P which, if maintained at steady state, will produce $A_J = At$.

At steady state we may write:

$$A_J k_{eo} = A_P k_{PJ}$$

In general:

$$A_J = \frac{C_P^{ss} k_{PJ} V_P}{k_{eo}} \qquad (3)$$

In particular:

$$At = \frac{C_P^{ss}{}_\theta k_{PJ} V_P}{k_{eo}}$$

$$\begin{bmatrix} Ae = \dfrac{C_P^{ss} k_{PJ} V_P}{k_{eo}} - At & \text{if } A_J > At \\ Ae = 0 & \text{otherwise} \end{bmatrix}$$

$$Ae_{50} = \frac{C_P^{ss}{}_{50} k_{PJ} V_P}{k_{eo}} - \frac{C_P^{ss}{}_\theta k_{PJ} V_P}{k_{eo}}$$

Thus equation (2) may be re-written:

$$E = \frac{\left[\dfrac{(C_P^{ss} - C_P^{ss}{}_\theta) k_{PJ} V_P}{k_{eo}}\right]^{\Gamma}}{\left[\dfrac{(C_P^{ss} - C_P^{ss}{}_\theta) k_{PJ} V_P}{k_{eo}}\right]^{\Gamma} + \left[\dfrac{(C_P^{ss}{}_{50} - C_P^{ss}{}_\theta) k_{PJ} V_P}{k_{eo}}\right]^{\Gamma}}$$

if $C_P^{ss} > C_P^{ss}{}_\theta$; $E = 0$ otherwise.

This simplifies to:

$$\begin{bmatrix} E = \dfrac{(C_P^{ss} - C_P^{ss}{}_\theta)^{\Gamma}}{(C_P^{ss} - C_P^{ss}{}_\theta)^{\Gamma} + (C_P^{ss}{}_{50} - C_P^{ss}{}_\theta)^{\Gamma}} & \text{if } C_P^{ss} > C_P^{ss}{}_\theta & (4) \\ E = 0 & \text{otherwise.} & (4) \end{bmatrix}$$

The expression for the amount of drug in compartment J at any time ($A_J(t)$) given in equation (1) may now be rewritten in terms of the steady state plasma concentration which would produce that value of A_J using equation (3).

Denote the steady state plasma concentration which will produce $A_J(t)$ by $C_P^{ss}(t)$. Then:

$$C_P^{ss}(t) = \frac{k_{eo}}{V_P k_{PJ}} \cdot k_{PJ} V_P e^{-k_{eo}t} \int_0^t C_P(T)\, e^{k_{eo}T}\, dT$$

This may be simplified:

$$C_P^{ss}(t) = k_{eo} e^{-k_{eo}t} \int_0^t C_P(T)\, e^{k_{eo}T}\, dT \qquad (5)$$

The derivation of the present model differs from that given by Sheiner and others [3] in three important respects:

(1) The proposal of a threshold plasma concentration below which no effect is produced. It may be noted that the present model reduces to the standard model if At is set to zero; for then $C_P^{ss}{}_\theta$ is zero and the terms related to the threshold in equation (4) disappear.

(2) k_{eo} is explicitly the sum of all exit processes from compartment J. The model is thus entirely applicable to atracurium, for which the question of drug elimination at peripheral sites arises.

(3) No definite relationship is proposed with any pharmacokinetic model, and pharmacokinetic parameters were not obtained

simultaneously with pharmacodynamic ones. This avoids the potential problem of mis-specification of the pharmacokinetic model affecting the interpretation of pharmacodynamic data, but dictates that equation (5) be handled numerically; this requires the estimation of the plasma atracurium concentration for each time point at which $C_P^{ss}(t)$ is to be estimated, and hence interpolation between the measured concentrations.

The scheme of interpolation used the predictions of the two-compartment model of best fit to the plasma concentration data set at all times except the first 2 min after the start of the infusion and the 2 min after the end of the infusion, at which times simple linear interpolation between the measured plasma concentrations was used. This scheme is convenient, yet preserves the form of the measured plasma concentration profile at times when circulatory delays imply that the measured and predicted concentrations might differ most.

Other schemes of interpolation, including simple linear interpolation between the measured plasma concentrations, and spline methods based on a series of second order polynomials, have been used and found to give almost identical results [19].

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DEPENDENCE OF THE NEUROMUSCULAR BLOCKING EFFECT OF ATRACURIUM UPON ITS DISPOSITION

C. J. R. PARKER AND J. M. HUNTER

SUMMARY

We have assessed the profiles of plasma concentration of atracurium and its neuromuscular blocking effect on the first response of the train-of-four measured by electromyography after a short infusion of atracurium 0.25 mg kg^{-1}, in 38 patients anaesthetized by one of three techniques. Measures of the temporal profile of neuromuscular block were found to correlate with pharmacokinetic variables. When anaesthetic technique was taken into account in a multivariate model, the time to onset of 10% depression of T1:T0 correlated positively with the central volume of distribution ($P < 0.05$). The change in T1:T0 during the 1 min after 10% depression, and the logit of maximum depression were both correlated negatively with the central volume of distribution ($P < 0.05$ and $P < 0.01$, respectively). Both the times to 20% and 50% recovery of T1:T0 correlated strongly negatively with clearance ($P < 0.0001$ for both measures). The findings support the conclusion that the effect of atracurium is dependent upon its disposition.

KEY WORDS

Neuromuscular relaxants: atracurium. Pharmacodynamics. Pharmacokinetics.

Whilst it is now generally assumed that the magnitude and duration of effect of the non-depolarizing neuromuscular blocking drugs are dependent upon the time course of their disposition, direct evidence for this supposition is scant. Early attempts by Aladjemoff, Dikstein and Shafrir [1] and by Cohen, Paulsen and Elert [2] to define the relationship between the plasma concentration of tubocurarine and its effects met with limited success because of the difficulty of the assay for tubocurarine, and the qualitative assessment of effect [1]. Matteo, Spector and Horowitz [3], in 1974, defined a correlation between the plasma concentration of tubocurarine and depression of the twitch tension of the adductor pollicis during recovery from a single dose, albeit with considerable scatter in individual results.

It was argued, however [4, 5], that such a correlation between plasma concentration and effect during recovery from a bolus of a neuromuscular blocking drug is only weak evidence for a causal dependence of effect upon disposition, as both plasma concentration and effect predictably decline in parallel during the recovery phase. The controversy surrounding this question has abated since the demonstration that tubocurarine and the nicotinic acetylcholine receptor dissociate over a time course of milliseconds, and the wide acceptance of a biophase model proposed by Hull and colleagues [6, 7] and by Sheiner and colleagues [8].

Perhaps the strongest evidence for a link between disposition and effect was provided for pancuronium by Shanks, Somogyi and Triggs [9], who demonstrated, in 27 patients, a strong positive correlation between the rate of recovery of the evoked twitch height and the elimination rate constant.

Although the biophase model has been applied to atracurium [10–14], the dependence of effect upon disposition has not been established for this drug. The main aim of the present study is to attempt to do so, in the paradigm of Shanks, Somogyi and Triggs [9].

PATIENTS AND METHODS

We studied 38 patients; all were healthy and undergoing elective minor surgery requiring the use of neuromuscular block. The study was approved by the Ethics Committee of the Royal Liverpool Hospital and informed consent was obtained from all patients. The patients were studied in three groups, which differed only in the technique used to maintain anaesthesia and were comparable for age, weight and sex (table I).

Premedication consisted of either promethazine 50 mg or diazepam 10 mg orally on the night before surgery, or cyclizine 37.5–50 mg with morphine 7.5–10 mg i.m. 1 h before surgery. In those patients admitted to hospital on the day of surgery, premedication was omitted.

Anaesthesia was induced with fentanyl 25–200 µg

TABLE I. *Physical characteristics of the patients in the three groups (mean (range or* SD*) or number)*

	Age (yr)	Weight (kg)	Sex (M:F)
Isoflurane ($n = 14$)	36.4 (19.7–65.1)	63.0 (11.3)	7:7
Halothane ($n = 14$)	39.7 (22.1–54.8)	67.4 (11.1)	6:8
Midazolam ($n = 10$)	37.3 (15.3–57.2)	66.8 (14.2)	4:6

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and thiopentone 250–500 mg, and maintained with 66 % nitrous oxide in oxygen. In one group this was supplemented with 0.9 % isoflurane (end-tidal); in a second group 0.5 % halothane (end-tidal) was used; in a third group no volatile anaesthetic agent was given, but the nitrous oxide in oxygen was supplemented with midazolam 3–10 mg i.v. End-tidal concentrations of volatile anaesthetic agents were monitored using an infra-red analyser (Datex "Normac").

After induction of anaesthesia, we commenced electromyographic monitoring of the height of the surface compound action potential of the adductor pollicis of one hand in response to supramaximal stimuli to the ulnar nerve. Trains of four stimuli at 2 Hz were repeated every 12.5 s throughout the study. The ratio of the height of the first response to the control height (T1:T0), and the ratio of the height of the fourth to the first response (T4:T1) were measured.

A cannula was placed in a vein in the antecubital fossa of the arm used for electromyographic monitoring, and used for obtaining blood samples. Another cannula was placed in a vein in the opposite forearm, for the administration of atracurium.

After a period of 20 min when the end-tidal concentration of volatile anaesthetic agent (if used) stabilized and the electromyographic baseline established, atracurium 0.25 mg kg^{-1} was given by constant rate infusion over a period of 10 min. Ventilation was controlled and the trachea intubated when appropriate; end-tidal carbon dioxide tension was maintained in the range 4.0–5.3 kPa (Datex "Capnomac").

Pharmacological antagonism of neuromuscular block was not used; neuromuscular monitoring was continued until both the ratios T1:T0 and T4:T1 were 80 % or greater (in one patient in the isoflurane group, electromyographic monitoring was discontinued when the ratio T1:T0 had recovered to 78.5 %). After recovery from neuromuscular block and the end of surgery, anaesthesia was discontinued, spontaneous ventilation re-established and the trachea extubated.

Heparinized blood samples (2.5 ml) were taken before and at 1, 2, 4, 6, 8 and 10 min after the start of the infusion, and at 1, 2, 4, 6, 8, 10, 15, 20, 25, 30, 40, 50, 60, 75 and 90 min after the end of the infusion. The samples were immediately acidified and cooled and the plasma separated promptly. The plasma was frozen rapidly in liquid nitrogen and stored at −20 °C until subsequent analysis. Three plasma samples were stored at each time; two were used for analysis of atracurium concentration in duplicate, one was held in reserve in case of technical problems.

An internal standard of tubocurarine 4 µg was added to each plasma sample, and the drugs were extracted from the plasma using solid phase cartridges with an active phenyl group ("Bond Elut"). At this time a standard curve was prepared which simulated plasma concentrations of atracurium 100, 200, 500, 1000 and 2000 ng ml^{-1}.

The extracted drug was assayed by high pressure liquid chromatography; an isocratic technique was used. Details of the column and mobile phase have been described previously [15]. A Perkin Elmer LS4 spectrofluorimeter, with a 3-µl flow cell was used for drug detection; the excitation wavelength was set to 280 nm and the detector to 320 nm. The method measures total plasma atracurium concentration, without separation of enantiomers.

The assay was sensitive to a plasma atracurium concentration of about 5 ng ml^{-1}. The coefficient of variation between duplicates varied between 1.6 % and 11.1 %, and was typically less than 6 %. The standard curve was linear; in no patient was the correlation coefficient for the standard curve less than 0.994, and it was usually greater than 0.998.

The heights of the first and fourth responses were measured for each train-of-four stimulus and T1:T0 calculated. The time course of the depression of T1:T0 was characterized by the summary measures shown in figure 1. These measures were chosen to indicate the time and rate of onset of block, of the maximum effect achieved, and of the time and rate of recovery.

Data analysis

In order to obtain estimates of the central volume of distribution and of the elimination half-life, equations arising from a pharmacokinetic model with two well-stirred compartments, with drug administration into and sampling from the central compartment, and with elimination allowed directly from both compartments, were fitted to the plasma concentration profile. As such a model is not uniquely identifiable [16], the following combination of parameters was identified:

V_1 = central volume of distribution
α = hybrid distribution rate constant
β = hybrid elimination rate constant
$k_{21} + k_{20}$ = sum of the rate constants for transfer of drug from the peripheral to the central compartment, and for direct elimination from the peripheral compartment, respectively.

These parameters were fitted to the data using the least squares criterion with each plasma concentration weighted as its inverse. Data obtained both during and after the end of the infusion were used simultaneously to fit the model, with the exception of the points 1 min after the start of the infusion and 1 min after its end, which were excluded; at these times, systematic discrepancy between the data and the model predictions was noted, which arose presumably from circulatory delay. The fit was obtained using the Gauss–Newton algorithm; partial derivatives were obtained numerically and convergence was accepted when each Gauss–Newton step changed the estimate of each parameter by less than 0.1 %.

The area under the curve (AUC) was calculated by the trapezoidal rule up to the last data point, together with the AUC extrapolated beyond the last data point using the previously estimated value of β. The area under the first moment curve (AUMC) was calculated in a similar manner. These areas were used to provide estimates of clearance and steady state volume of distribution using standard formulae [17].

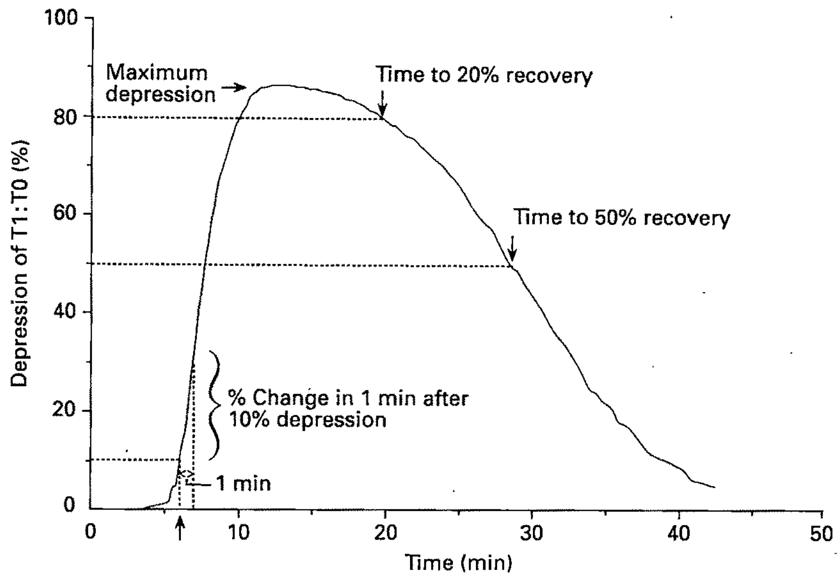

FIG. 1. Measures of the time course of the depression of the first response of the train-of-four (T1:T0). Times are measured from the start of the atracurium infusion. ↑ = Time to 10 % depression.

The possible relationship between each of the measures of effect and measures of disposition was explored initially by calculation of Pearson's correlation coefficient. Multivariate regression, with two dummy parameters to separate the groups, was applied to allow account to be taken of the influence of anaesthetic technique upon the measure of effect. Thus the linear multivariate model was fitted:

$$y = \alpha_0 + \beta_1 x + \beta_2 i + \beta_3 h + \varepsilon$$

where y = effect variable of interest, e.g. time to 50 % recovery; x = a pharmacokinetic variable, e.g. clearance; α_0 = an intercept; β_1 = slope of the relationship between y and x; i and h = dummy variables which take the value 1 if the patient received isoflurane or halothane respectively, and 0 otherwise; β_2 and β_3 = corresponding regression coefficients; ε = residual error not explained by the regression model; its size forms the basis of comparison between alternative regression models.

Added variable plots [18] were used to illustrate graphically the dependence of an effect variable on a pharmacokinetic variable in the multivariate context. This is a plot of the residuals (ε) of the regression for the model without the added variable (i.e. without the $\beta_1 x$ term above), plotted against the residuals of the regression of the added variable on the explanatory variables already in the model (i.e. the residuals of the regression of x on the dummy variables h and i above). The slope of the relationship between these two sets of residuals is equivalent to β_1; the strength of the correlation between the two sets of residuals represents the strength of the relationship between y and x in the multivariate model above.

RESULTS

The measures of the time course of depression of T1:T0 are summarized, together with pharmacokinetic measures, in table II.

The plasma atracurium concentration profile for each group is given as mean (SD) at each time in figure 2.

The univariate correlation coefficient between each of the measures of the depression of T1:T0 and each of the measures of disposition is shown in table III. Of the 30 possible comparisons, eight achieved statistical significance at the 5 % level. There was no significant correlation between any of the measures of effect and either $T_{\frac{1}{2}}^{\beta}$ or the rate constants α or $k_{21} + k_{20}$.

The positive findings have been analysed further.

Time to 10 % depression of T1 : T0

When all patients are considered together, the time to 10 % depression correlated positively with the central volume of distribution ($r = +0.33$; 36 d.f.; $P < 0.05$) (fig. 3).

Taking account of the anaesthetic technique in a multivariate regression clarifies the strength of the relationship between the time to 10 % depression of T1:T0 and the central volume of distribution ($F = 5.68$; 1,34 d.f.; $P < 0.05$).

Change during 1 min after 10 % depression of T1 : T0

Amongst all the patients, the percentage change during the 1 min after the achievement of 10 % depression of T1:T0 correlated negatively with the central volume of distribution ($r = -0.34$; $P < 0.05$). Multivariate regression with separation of the three groups revealed a stronger underlying relationship ($F = 7.34$; 1,34 d.f.; $P < 0.05$).

Maximum block

As the data for maximum block had a variance which is not homogeneous between groups (table II), the logit transformation was applied before correlation with indices of disposition was attempted. There was a weak negative correlation with the central volume of distribution ($r = -0.32$; 36 d.f.; $0.05 < P < 0.1$). Taking account of the anaesthetic technique, multivariate analysis revealed a strong relationship ($F = 11.5$; 1,34 d.f.; $P < 0.01$).

TABLE II. *Measures of the time course of depression of T1 : T0 of the train-of-four, and measures of the pharmacokinetic profile for each group (mean (SD))*

	Isoflurane ($n = 14$)	Halothane ($n = 14$)	Midazolam ($n = 10$)
Pharmacodynamics			
Time to 10% depression (min)	4.3 (0.6)	4.2 (0.6)	4.8 (0.9)
Change in the 1 min after 10% depression (%)	32.6 (5.9)	32.1 (7.9)	27.8 (6.0)
Maximum depression (%)	97.0 (1.4)	95.8 (2.1)	93.8 (4.5)
Logit maximum depression	1.56 (0.21)	1.42 (0.25)	1.26 (0.32)
Time to 20% recovery (min)	34.7 (6.0)	34.9 (6.8)	29.2 (7.8)
Time to 50% recovery (min)	45.6 (7.5)	45.3 (8.6)	39.0 (8.0)
Pharmacokinetics			
V_1 (ml kg^{-1})	72.2 (12.6)	58.3 (10.2)	62.6 (21.7)
V^{ss} (ml kg^{-1})	141 (21.4)	120 (15.7)	125 (37.1)
Clearance (ml min^{-1} kg^{-1})	6.9 (1.1)	5.4 (0.7)	5.8 (1.0)
$T_{\frac{1}{2}}^{\beta}$ (min)	18.8 (2.8)	20.2 (3.2)	19.4 (3.2)
α (min^{-1})	0.26 (0.12)	0.24 (0.06)	0.24 (0.06)
$k_{21} + k_{20}$ (min^{-1})	0.10 (0.04)	0.09 (0.02)	0.09 (0.02)

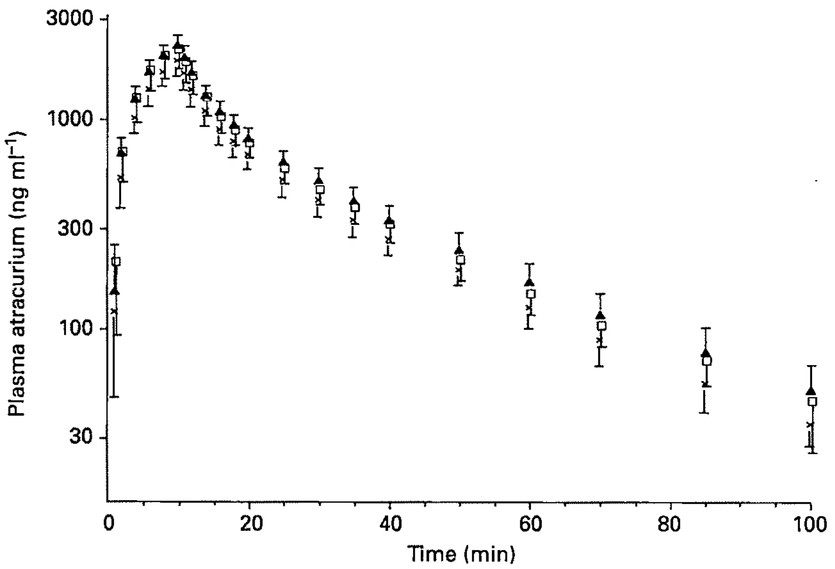

FIG. 2 Mean (SD) plasma concentration of atracurium at each time point for the isoflurane (×), halothane (▲) and midazolam (□) groups. For clarity, the points for the isoflurane group have been displaced to the left by 0.2 min and those for the midazolam group to the right by 0.2 min.

TABLE III. *Univariate correlation between each of the measures of disposition and each of the descriptors of effect on T1 : T0. Values shown are those for Pearson's product moment correlation coefficient, in each instance with 36 degrees of freedom. Eight significant correlations from amongst the 30 possible :* *P < *0.05;* **P < *0.01*

	V_1	V^{ss}	Clearance	$T_{\frac{1}{2}}^{\beta}$	α	$k_{21} + k_{20}$
Time to 10% depression	+0.33*	+0.29	+0.22	+0.10	−0.18	−0.12
Change in the 1 min after 10% depression	−0.34*	−0.24	−0.13	−0.09	+0.26	+0.16
Logit maximum depression	−0.32	−0.25	−0.15	−0.08	+0.22	+0.15
Time to 20% recovery	−0.40*	−0.38*	−0.48**	+0.19	−0.05	−0.17
Time to 50% recovery	−0.35*	−0.33*	−0.48**	+0.26	−0.11	−0.24

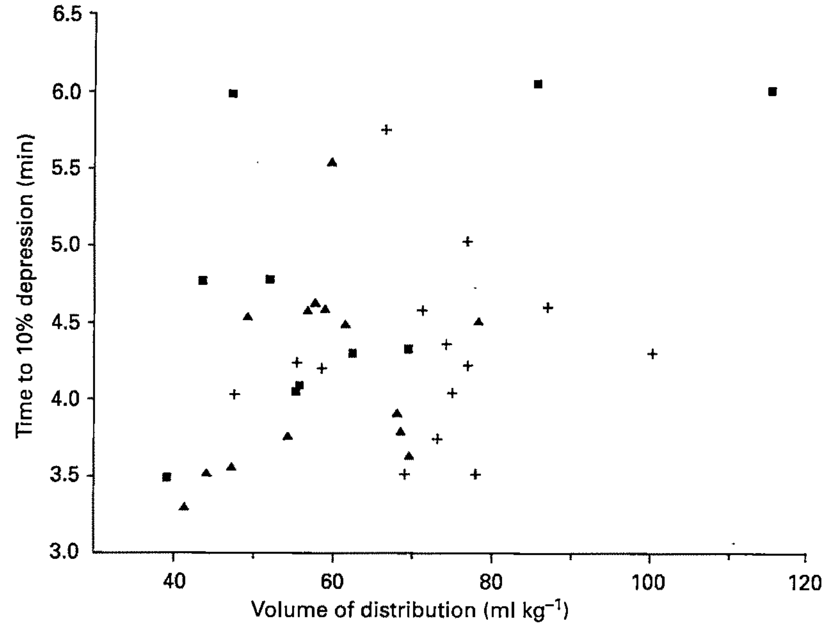

FIG. 3. Time to 10% depression of T1:T0 plotted against central volume of distribution for each patient. There is a positive correlation ($r = +0.33$; $P < 0.05$). + = Isoflurane group; ▲ = halothane group; ■ = midazolam group.

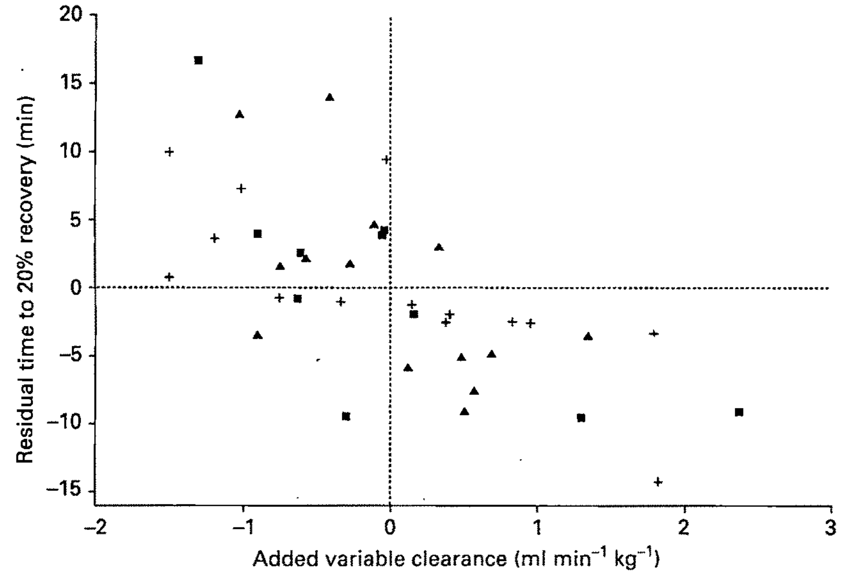

FIG. 4. Relationship between time to 20% recovery of T1:T0 and clearance, when anaesthetic technique is taken into account in a multivariate regression: added variable plot of the residuals of the regression of time to 20% recovery on group *vs* residuals of the regression of clearance on group. The plot demonstrates the strong negative correlation between time to 20% recovery and clearance ($F = 28.7$; $P < 0.0001$). + = Isoflurane group; ▲ = halothane group; ■ = midazolam group.

Time to 20% recovery of T1 : T0

The time from the start of the infusion of atracurium to 20% recovery of T1:T0 correlated negatively with both measures of volume of distribution, but even more strongly with clearance ($r = -0.48$; 36 d.f.; $P < 0.01$). When the difference between the three groups was taken into account using multivariate regression, the relationship was strong ($F = 28.7$; 1,34 d.f.; $P < 0.0001$). The negative correlation between time to 20% recovery and clearance is shown by the added variable plot in figure 4.

Time to 50% recovery of T1 : T0

The results for time to 50% recovery of T1:T0 paralleled those for the time to 20% recovery. There was a univariate negative correlation with clearance ($r = -0.48$; 36 d.f.; $P < 0.01$). When the groups were separated in a multivariate regression the underlying relationship was strong ($F = 31.7$; 1,34 d.f.; $P < 0.0001$).

DISCUSSION

Several groups have defined the pharmacodynamics and pharmacokinetics of atracurium, and data on the effect and disposition of atracurium have been united formally in five reports [10–14]. In all these studies, the measured effect and plasma concentration profiles were used to find the parameter values which provided the best fit of a biophase model with a predetermined structure. Whilst making the maximal use of the data gathered from the study of a single subject, this powerful method of analysis takes the structure of the model as given. Of course, the model is not a perfect representation of the patient, and in practice the data contain errors; consequently, the pharmacodynamic data and the predictions of the model of best fit do not match perfectly. The issue as to how much discrepancy may be present before the model is re-evaluated has not been examined for atracurium.

The present approach is radical: no prior assumptions have been made on the structure or even the existence of a link between the disposition and effect of atracurium. The pharmacokinetic and pharmacodynamic analyses were carried out independently; the attempt to find a link between the two data sets was carried out at the level of the whole population. This exploratory approach has certain weaknesses.

One potential criticism is that only positive results have been presented in detail; this criticism is ameliorated by several considerations. First, some of the correlations presented are extremely strong. As five summary measures of effect were tested for correlation with each of the six summary pharmacokinetic measures here calculated, 30 correlations were possible. Thus there is still less than a 1 in 300 chance of finding a correlation as strong as that which was found to exist in the multivariate context between the time to 20% recovery and clearance.

Second, the somewhat arbitrary summary measures of both effect and disposition are themselves correlated. Thus the tests of the relationship between, say, the clearance and both the times to 20% and to 50% recovery are not totally independent, and correction of the significance levels on the assumption that the comparisons were independent would be too harsh.

Third, the correlations presented are feasible. In a review of the relationship between the pharmacokinetics and pharmacodynamics of the non-depolarizing neuromuscular blocking drugs in 1984, Hennis and Stanski [19] listed the central volume of distribution as one of the factors which affects onset time; they cited pharmacokinetic results obtained in patients with cirrhosis but failed to cite any evidence that onset time is increased in this group. The present report provides the first firm evidence for a link between the central volume of distribution and time to onset of block from atracurium. The stronger negative correlations between times to 20% and 50% recovery and clearance are also feasible, for it seems reasonable that a high rate of plasma clearance should be associated with a rapid recovery.

Finally, graphical analysis of the results illustrates that the correlations detected by formal analysis reflect the data as a whole, and do not represent solely the influence of one or two outlying individuals.

The use of multivariate regression allowed the results from a larger number of patients to be compared more directly than might otherwise have been the case. Two extra parameters were included in the multiple regressions to separate the three groups in view of the prior knowledge that the volatile anaesthetic agents halothane and isoflurane potentiate non-depolarizing neuromuscular blocking drugs, and to a different degree [20].

The measures of the time course of depression of the ratio T1:T0 chosen for analysis here are rather arbitrary. Conceivably, the choice of somewhat different measures might have yielded slightly different results. However, the five measures chosen span the majority of the time course, from the onset of 10% depression to 50% recovery. In addition, the time to onset of effect and maximum block are measures of some practical importance. The maximum block is a measure of effect used frequently, and is used sometimes as the sole measure [20]. Different measures of the temporal profile of effect would not have produced different conclusions.

It is, unfortunately, not possible to use the present results to enable prediction of the response of future individual patients; variability in the population would make such an estimate prone to considerable error. However, the present report has defined, within a large population of subjects, relationships between the disposition and effect of atracurium which are statistically very strong, which are feasibly compatible with prior understanding, and yet which do not depend upon the validity of any particular structural model. They are the first of their kind to be reported for atracurium and they form a necessary preliminary to the definition of a structural model of the pharmacodynamics of atracurium.

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HALOTHANE DOES NOT DEPRESS CONTRACTILE FUNCTION OF FRESH OR FATIGUED DIAPHRAGM IN PENTOBARBITONE-ANAESTHETIZED DOGS

T. KOCHI, T. IDE, T. MIZUGUCHI AND T. NISHINO

SUMMARY

We have studied the effect of halothane on diaphragmatic contractile function by measuring transdiaphragmatic pressure (Pdi) and electromyogram of the diaphragm (Edi) during various stimulation frequencies in 15 pentobarbitone-anaesthetized dogs undergoing mechanical ventilation. We have examined also the effect of halothane on the fatigued diaphragm by repeating the measurements 5, 10, 15, 30, 60 and 90 min after 30 min of tetanic stimulation applied to the phrenic nerves. Administration of 1–2 MAC of halothane did not affect Pdi at any given stimulation frequency. Changes in the depth of halothane anaesthesia (0, 1 and 2 MAC) did not alter the force–frequency relationship of the diaphragm during recovery from fatigue. Edi was unaffected by halothane, except for a small decline during 100-Hz stimulation with 2 MAC. In contrast with the changes in Pdi, Edi during recovery from fatigue was the same as that determined before fatigue. It is concluded that halothane, in clinical concentrations, did not depress the contractile function of fresh or fatigued diaphragm in vivo.

KEY WORDS

Anaesthetics, volatile: halothane. Muscle, skeletal: diaphragm, contractility.

The effects of various inhalation anaesthetics on the contractile performance of the diaphragm have been examined recently *in vivo* [1–4]. In dogs undergoing mechanical ventilation, it has been found that enflurane impairs diaphragmatic function in a dose-dependent manner, while halothane had little or no effect at equivalent anaesthetic depth [3]. However, these observations conflict with findings in spontaneously breathing dogs, in which halothane depressed both transdiaphragmatic pressure generation and electrical activity of the diaphragm in response to electrophrenic stimulation [1]. Such halothane-induced impairment of diaphragmatic function may be related in part to halothane-induced reduction of perfusion pressure, resulting in a reduction in effective substrate supply. In addition, the energy demands should be greater with halothane as a result of a greater ventilatory frequency which would be expected to increase the diaphragmatic tension–time index. Moreover, the concomitant decrease in arterial pH and increase in Pa_{CO_2} may affect the contractile process of the diaphragm [5, 6].

It has been demonstrated that halothane enhances the action of non-depolarizing neuromuscular blocking agents and consequent effects on respiratory muscles [7]. Therefore it may also affect the contractile function of the fatigued diaphragm.

In the present study, we have investigated the effect of halothane on diaphragmatic function in pentobarbitone-anaesthetized dogs undergoing mechanical ventilation. Furthermore, to test the above hypothesis, we have examined the effect of halothane on the fatigued diaphragm.

MATERIALS AND METHODS

Approval for the study was obtained from the Animal Care and Use Committee of Chiba University School of Medicine. Fifteen mongrel dogs (10–12 kg) were anaesthetized with sodium pentobarbitone 30 mg kg^{-1} i.v. The trachea was intubated with a cuffed tracheal tube and anaesthesia was maintained with a continuous infusion of pentobarbitone 4 mg kg^{-1} h^{-1}. The dogs were placed in supine position and the lungs ventilated mechanically with 100% oxygen throughout the experiment. Tidal volume was set to 15 ml kg^{-1} and ventilatory frequency adjusted to 10–15 b.p.m. in order to maintain normal Pa_{CO_2} (4.0–5.3 kPa). The left femoral artery was cannulated in order to measure arterial pressure and obtain blood samples for measurement of arterial blood-gas tensions using an IL blood gas analyser (Instrumentation Laboratories, model 1302). The left femoral vein was cannulated also for administration of fluids and bicarbonate to correct acidosis. Rectal temperature was monitored continuously and maintained at 37–38 °C via external heating.

The preparation used is shown schematically in figure 1. An oesophageal balloon catheter was placed in the lower one-third of the oesophagus. A similar

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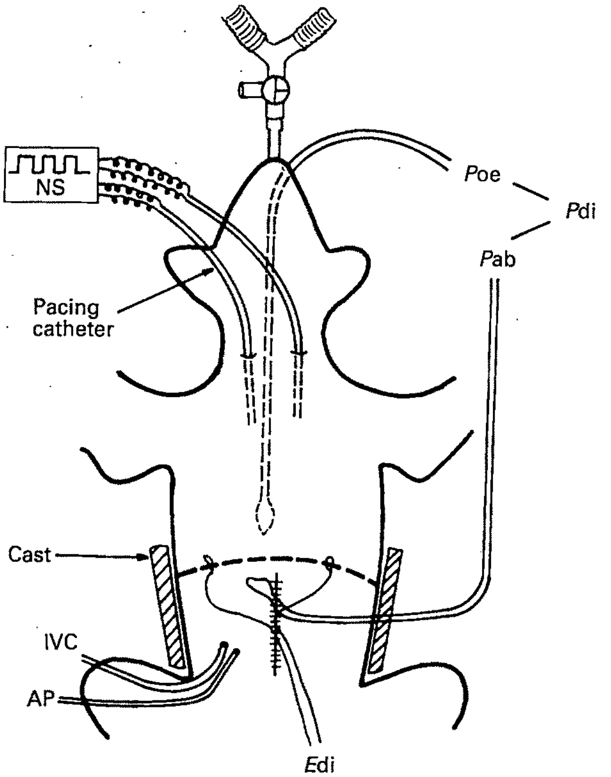

FIG. 1. Schematic illustration of the animal preparation. NS = Nerve stimulator; *P*oe = oesophageal pressure; *P*ab = abdominal pressure; *P*di = transdiaphragmatic pressure; IVC = i.v. cannula; AP = arterial pressure; *E*di = electromyographic electrode hooked to diaphragm.

balloon catheter was placed beneath the costal part of the diaphragm through an upper abdominal incision. Transdiaphragmatic pressure (*P*di) was measured by connecting the proximal ends of these two balloon catheters to each side of a differential pressure transducer (Nihon Kohden TP-604T). Two i.v. cardiac pacing catheters were inserted via the jugular veins into the superior vena cava. The tip of the catheter was positioned where maximum twitch response could be obtained upon electrical stimulation of each phrenic nerve. Two fish-hook type electrodes were inserted into the costal parts of each hemidiaphragm and connected to a preamplifier (Nihon Kohden EI-601G) for measurement of the diaphragmatic electromyogram (EMG). The EMG signal was amplified and rectified through a leaky integrator (Nihon Kohden AB-621G) to obtain the integrated EMG of the diaphragm (*E*di). The abdominal incision was closed tightly in layers after placing the abdominal catheter and EMG electrodes. The phrenic nerves were stimulated using an electric stimulator (Nihon Kohden SEN-3201). Single twitch stimulations were applied first, followed by 2-s periods of stimulations applied at frequencies of 10, 20, 50 and 100 Hz. During stimulations, mechanical ventilation was halted and the airways were occluded at end-expiration, to avoid changes in lung volume during diaphragmatic contraction. Furthermore, constancy of diaphragmatic length and thoraco-abdominal configuration was achieved by placing a closely fitted plaster cast around the abdomen and lower one-third of the rib cage [8].

The animals were allocated randomly to three groups of five dogs according to end-expiratory concentration of halothane: 0 MAC in group 1, 1 MAC in group 2, and 2 MAC in group 3. Halothane was administered using a continuous-flow Acomatec vaporizer (Acoma, Japan), and end-expiratory concentration of halothane was measured continuously with an infra-red analyser (Normac, Datex). The same procedure was followed in all animals. After completion of the control measurements, halothane was added to the inspired gas in groups 2 and 3. After 1 h of halothane exposure, diaphragmatic function was reassessed. In group 1 animals, the measurement was repeated 1 h after the initial control measurements, then the phrenic nerves were stimulated supramaximally (pulse duration 0.2 ms, frequency 30 Hz, amplitude 30 V) for 30 min to induce diaphragmatic fatigue [9]. After this, diaphragmatic function was reassessed after 5, 10, 15, 30, 60 and 90 min to examine recovery from fatigue.

All values are presented as mean (SEM). Intragroup and intergroup differences at different times of the study were compared using two-way analysis of variance and Tukey's test. The level of statistical significance was set at $P < 0.05$.

RESULTS

Arterial pressure decreased significantly during halothane exposure, while pH and blood-gas tensions were unchanged, regardless of the level of anaesthesia (table I).

TABLE I. *Mean values* (SEM) *of mean arterial pressure* (*MAP*), *arterial pH, carbon dioxide tension* (Pa_{CO_2}) *and oxygen tension* (Pa_{O_2}) *of three groups of animals during control period and after administration of halothane. Significant differences compared with control:* *$P < 0.05$; **$P < 0.01$

	Control			Halothane		
	Group 1 (Pentobarbitone alone)	Group 2 (Pentobarbitone alone)	Group 3 (Pentobarbitone alone)	Group 1 0 MAC	Group 2 1 MAC	Group 3 2 MAC
MAP (mm Hg)	147	125	141	148	101*	80**
	(6.5)	(7.7)	(5.4)	(9.7)	(8.3)	(4.3)
pH	7.38	7.38	7.37	7.37	7.37	7.38
	(0.02)	(0.02)	(0.01)	(0.01)	(0.02)	(0.02)
Pa_{CO_2} (kPa)	5.0	4.5	4.8	5.0	4.8	4.7
	(0.3)	(0.3)	(0.2)	(0.3)	(0.2)	(0.3)
Pa_{O_2} (kPa)	60.3	59.0	60.2	61.4	57.3	61.4
	(4.0)	(6.6)	(3.7)	(3.2)	(5.7)	(3.4)

TABLE II. *Mean (SEM) values of transdiaphragmatic pressure (*Pdi*) for three groups of animals*

Stimulation frequency (Hz)	Transdiaphragmatic pressure (cm H_2O)					
	Control			Halothane		
	Group 1	Group 2	Group 3	Group 1	Group 2	Group 3
	(Pentobarbitone alone)			(0 MAC)	(1 MAC)	(2 MAC)
0.5	13.0	12.9	14.0	12.7	13.5	14.0
	(2.0)	(1.6)	(2.5)	(2.1)	(1.4)	(2.8)
10	15.8	13.2	14.4	15.0	14.4	14.0
	(3.9)	(2.6)	(2.0)	(3.9)	(2.4)	(1.6)
20	45.6	43.6	46.4	43.2	46.1	44.0
	(7.5)	(3.6)	(5.4)	(7.6)	(3.5)	(4.7)
50	59.3	59.6	64.4	56.5	59.2	57.8
	(9.9)	(5.1)	(9.6)	(9.0)	(5.4)	(7.7)
100	57.3	61.3	65.0	55.2	61.0	57.8
	(9.3)	(5.9)	(9.4)	(9.0)	(5.9)	(7.7)

TABLE III. *Mean (SEM) values of electromyographic activity of the diaphragm (*Edi*) after exposure to halothane during various frequencies of electrophrenic stimulations for three groups of animals. (expressed as percentage of control *Edi*). $^*P < 0.05$*

Stimulation frequency (Hz)	*E*di (% of control)		
	Group 1 (0 MAC)	Group 2 (1 MAC)	Group 3 (2 MAC)
0.5	100.6	100.1	99.5
	(3.7)	(4.7)	(1.5)
10	106.5	97.2	97.4
	(7.7)	(3.5)	(2.1)
20	98.1	96.8	104.2
	(3.5)	(4.7)	(9.0)
50	99.4	102.3	94.8
	(4.8)	(6.4)	(7.3)
100	100.2	95.2	84.9*
	(4.9)	(3.4)	(8.3)

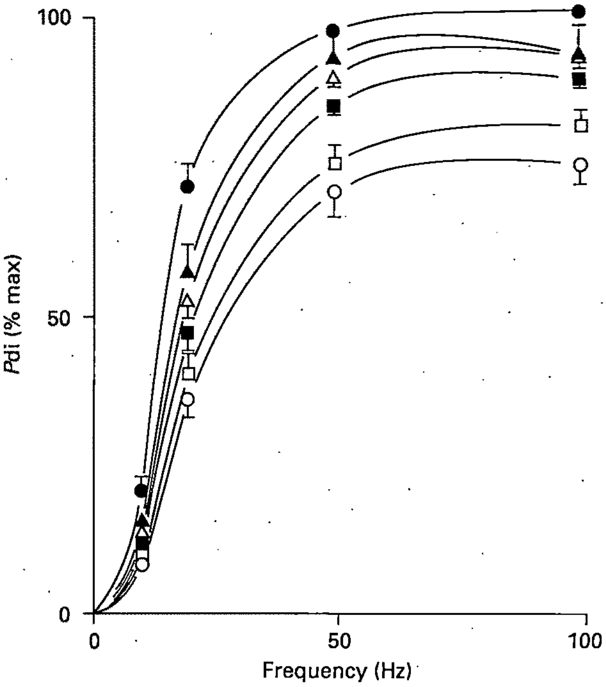

FIG. 2. Mean (SEM) force–frequency relationships of the diaphragm in group 2 (1 MAC) animals: control (●) and 5 (○), 15 (□), 30 (■), 60 (△) and 90 (▲) min after fatigue. *P*di is expressed as percent of maximum *P*di value obtained under control conditions.

The effects of the three different concentrations of halothane on *P*di are summarized in table II. No significant difference between groups was observed during control readings and 1 h after 1 or 2 MAC of halothane exposure. Halothane 1 MAC did not affect *E*di at any stimulation frequency; 2 MAC did not alter *E*di at frequencies between 0.5 and 50 Hz; *E*di at 100-Hz stimulation was depressed significantly compared with both 0 and 1 MAC (table III).

In all animals, 30 min tetanic stimulation reduced *P*di markedly at all stimulation frequencies (fig. 2). The relative changes in *P*di after fatigue were greater at low than at high frequency stimulations. The amplitude of *P*di returned gradually toward the value before fatigue, but recovery was not complete even by 90 min. In marked contrast with the changes

TABLE IV. *Relative changes (mean (SEM)) in transdiaphragmatic pressure (*Pdi*) during low (20-Hz) and high (100-Hz) frequency stimulation for three groups of animals during recovery from fatigue*

	*P*di (% of control)							
	Low frequency stimulation (20 Hz)				High frequency stimulation (100 Hz)			
	5 min	30 min	60 min	90 min	5 min	30 min	60 min	90 min
Group 1	52.5	59.9	62.9	70.3	74.2	88.7	83.5	92.4
	(5.7)	(4.2)	(7.1)	(5.2)	(4.3)	(3.8)	(6.1)	(2.2)
Group 2	50.3	65.7	73.5	80.2	74.5	88.7	92.6	93.3
	(5.1)	(4.1)	(4.6)	(4.9)	(3.9)	(1.9)	(2.5)	(5.4)
Group 3	52.1	66.4	75.4	78.7	60.8	74.6	78.1	76.9
	(5.8)	(7.0)	(6.5)	(6.3)	(6.2)	(4.2)	(3.1)	(3.3)

in *P*di, the amplitude of *E*di following fatigue was similar to the value before fatigue at all stimulation frequencies.

To quantify the changes in *P*di between groups during low and high frequency stimulations, the percent changes in *P*di (control *P*di = 100%) after 5, 30 and 90 min were calculated for 20 and 100 Hz. The relative changes in *P*di were greater during 20-Hz compared with 100-Hz stimulation in all three groups (table IV). However, the magnitude of the percentage reduction in *P*di was not statistically different between the three groups of animals during 20-Hz or 100-Hz stimulations.

DISCUSSION

The main findings of this study were that halothane did not affect the contractile function of non-fatigued canine diaphragm at concentrations up to 2 MAC, and that halothane had little effect on the fatigued diaphragm *in vivo*. The absence of depressant effects of halothane on the contractile properties of the non-fatigued canine diaphragm is in agreement with our previous results [3]. However, this is in contrast with observations of Clergue and colleagues [1] in spontaneously breathing dogs, that halothane reduced force generation and EMG of the diaphragm in response to phrenic nerve stimulation at all stimulation frequencies.

The differences between our results and those of Clergue and colleagues may be explained by differences in methodology. Differences in ventilation (mechanical ventilation *vs* spontaneous breathing) may have affected the contractile function of the diaphragm, as diaphragmatic energy supply and demand relationships are affected by the mode of ventilation [8]. Furthermore, in our study, a closely fitted cast was placed around the lower rib cage and the abdomen: Clergue's group did not use a cast. Therefore, their results may have been influenced by changes in abdominal expiratory muscle activity [9, 10] and in abdominal compliance with varying anaesthetic depth. In addition, without a cast, the diaphragm does not contract isometrically. The value of *P*di is influenced not only by contractility but also by resting length and shape of the diaphragm [11].

Finally, the increased ventilatory frequency during halothane administration may have increased the diaphragmatic tension–time index and may have predisposed it to muscle fatigue.

In the present study, we avoided the influences of changing acid–base status, and varying length and geometry of the diaphragm. Thus we have examined the effect of halothane on the diaphragmatic contractile performance in isolation.

It has been demonstrated in anaesthetized man that administration of 1–2% halothane during recovery from neuromuscular block reduced the peak contraction of the tetanic response of the adductor pollicis muscle and increased tetanic fade [7]. Thus, if fatigue phenomenon and neuromuscular transmission failure share common mechanisms, halothane would enhance the degree of muscle fatigue. However, our results show that increasing depth of halothane anaesthesia did not affect either the force–frequency relationships or *E*di both before and after fatigue, except for a small decline in *E*di at 100 Hz stimulation in group 3 (2 MAC) animals after halothane exposure. This indicates that, unlike its synergistic effects with non-depolarizing neuromuscular blocking agents, halothane did not alter the contractile function of fresh and fatigued diaphragm, at least under the present experimental conditions.

In open chest rats and dogs undergoing artificial ventilation, isoflurane, enflurane and servoflurane produced depression of diaphragmatic tension during high frequency stimulation (50, 100 Hz) [2–4]. Such decreases in tension during high frequency stimulations are considered to reflect impaired neuromuscular transmission, blunted membrane excitation, or both [12, 13]. These *in vivo* results are in agreement with the findings obtained *in vitro* on lumbrical muscle of the guineapig [14]. To the extent that such *in vitro* results can be applied *in vivo*, lack of impairment of diaphragmatic function during halothane anaesthesia (1–2 MAC) would be expected.

In conclusion, our data demonstrate preservation of the contractile function of both fresh and fatigued diaphragm during halothane anaesthesia. This, together with the potent action of halothane on bronchial smooth muscle, may favour the use of halothane in the anaesthetic management of patients with chronic obstructive airway disease whose respiratory muscles are at risk of fatigue.

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NEUROMUSCULAR BLOCKING ACTIVITY OF TUBOCURARINE IN PATIENTS WITH DIABETES MELLITUS†

M. M. ATALLAH, A. A. DAIF, M. M. A. SAIED AND Z. M. SONBUL

SUMMARY

Previous clinical reports have suggested that deep tendon reflexes of diabetic patients are delayed and experimental studies have reported differential sensitivity of motor endplates to neuromuscular blocking drugs. These observations prompted us to study the neuromuscular effect of tubocurarine in 25 diabetic and 15 non-diabetic patients during urological surgery. Anaesthesia was induced with thiopentone followed by suxamethonium and maintained with nitrous oxide in oxygen and increments of butorphanol. Muscle relaxation was provided with tubocurarine in an initial dose of 0.25 mg kg^{-1} and increments of 20% of the initial dose. At the end of surgery, residual neuromuscular block was antagonized with increments of neostigmine 0.5 mg and atropine 0.2 mg. There was a delay in the onset of action of tubocurarine in diabetic patients. A no-response state was obtained in some patients, and its duration correlated with post-tetanic count (PTC) in diabetic patients, and with post-tetanic twitch height percent (PTTH%) in the control group. We concluded that, in diabetic patients, the onset of action of tubocurarine was delayed compared with control patients, and the reliable predictor of the duration of the no-response time was PTC in diabetic patients and PTTH% in non-diabetic subjects.

KEY WORDS

Complications: diabetes mellitus. Neuromuscular relaxants: tubocurarine.

Although neuromuscular problems are common in patients with diabetes mellitus, there are few studies on the activity of the neuromuscular junction in such patients. In isolated diaphragm muscle of diabetic mice, it was found that the acetylcholine potential amplitude was greater than in control diaphragms [1]. In clinical studies, a delay in deep tendon reflexes of patients with diabetes mellitus has been reported [2–4].

Experimental studies have demonstrated a differential sensitivity of motor endplates to commonly used neuromuscular blocking drugs [1, 5–7]: sensitivity to tubocurarine was decreased in diabetic rats, while the response to suxamethonium was increased [5]. This increased sensitivity to suxamethonium was reported later in cross-culture preparations of skeletal muscles of diabetic mice [6], and confirmed in *in vivo* and *in vitro* preparations of diabetic mice, whilst diminished activity of tubocurarine could not be confirmed [1].

To our knowledge, there have been no clinical studies reporting changes in the activity of neuromuscular blocking drugs in diabetic patients. This study was designed to examine the activity of tubocurarine in maturity-onset, type II diabetes mellitus patients and compared the effects with those in normal subjects.

PATIENTS AND METHODS

This was an open study, in 40 patients undergoing a variety of urological operations. We studied 25 patients suffering from type II diabetes mellitus and 15 non-diabetic patients as a control group. The diabetic patients were treated with oral hypoglycaemic agents and these were replaced, the day before operation, by soluble insulin. Patients were excluded if they had acidosis, hepatic or renal impairment, neuromuscular disease or familial history of hereditary neuromuscular disorders. The study was approved by the local Ethics Committee and informed consent was obtained from all participants.

Premedication comprised diazepam 0.15 mg kg^{-1} and butorphanol 30 μg kg^{-1} i.v. 10 min before anaesthesia, which was induced with thiopentone 5 mg kg^{-1} and atropine 0.5 mg. Tracheal intubation was facilitated with suxamethonium 1 mg kg^{-1}. Anaesthesia was maintained with 66% nitrous oxide in oxygen, supplemented with butorphanol 10 μg kg^{-1} if necessary. Neuromuscular block was achieved by tubocurarine in an initial dose of 0.25 mg kg^{-1} and incremental doses of 20% of the initial dose. At the end of surgery, residual neuromuscular block was antagonized with neostigmine in incremental doses of 0.5 mg mixed with atropine 0.2 mg, given at 5-min intervals.

The ulnar nerve was stimulated via two surface electrodes proximal to the wrist joint (Myotest). A rectangular stimulus of 0.2 ms duration and maxi-

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mum amplitude 60 mA was used. Contraction of the adductor policis brevis muscle was measured using a force-displacement transducer (TD 100, Myograph 2000, Biometer, Denmark).

Immediately after induction of anaesthesia, supramaximal stimuli were applied to the ulnar nerve at a rate of 1 Hz until the twitch height was stable, indicating recovery from the effect of suxamethonium. This was considered the baseline height (100%). The pattern of stimulation was then changed to train-of-four (TOF) before administration of the initial dose of tubocurarine 0.25 mg kg^{-1}. TOF stimulation was recorded every 12 s until the twitch height (first response of TOF) was steady (for five successive responses) or zero. TOF stimulation was continued at steady state every 1-min until the twitch height exceeded 10% of the baseline value, when an incremental dose of tubocurarine was given. If a no-response state (no response to single, tetanic or TOF) was reached after the initial dose of tubocurarine, tetanic stimulation (50 Hz) was applied for 5 s. This was followed by a 3-s pause and then single stimuli (1 Hz) until the pretetanic no-response state was reached. Post-tetanic count and post-tetanic twitch height were recorded. TOF stimulation was continued at 1-min intervals until the first response appeared.

Administration of tubocurarine was stopped towards the end of surgery and spontaneous recovery was allowed to develop to a TOF ratio of 25%. Neostigmine in incremental doses of 0.5 mg and atropine 0.2 mg were given at 5-min intervals until the TOF ratio was 70%.

The following variables were measured: onset of relaxation (time from initial injection of tubocurarine until 10% of the basal twitch height was attained); zero time (time from injection of tubocurarine until zero TOF ratio); duration of relaxation (time from initial injection of tubocurarine until a twitch height of 10% of the baseline value was regained); post-tetanic count (PTC) (number of twitches after a tetanic stimulation of 50 Hz for 5 s, and elicited by stimuli at a frequency of 1 Hz before it reached the pretetanic no-response state again); post-tetanic twitch height percent (PTTH%) (percent of the height of the first post-tetanic twitch to the height of the basal twitch); recovery time (time for recovery of TOF ratio from 25% to 70%); no response time (NRT) (time from tetanic stimulation to first response to TOF stimulation); total dose of tubocurarine (doses of tubocurarine divided by body weight and total duration of relaxation); total dose of neostigmine (sum of the incremental doses of neostigmine used to induce recovery from 25% to 70% TOF ratio divided by body weight).

Statistical analysis

Variables are displayed as mean (SD). Differences between similar variables in the two groups were analysed by Student's *t* test and the level of significance was taken as $P < 0.05$. Correlation tests were used to detect the degree of correlation between different variables in the same group. Multiple regression analysis using a computerized statistical package (SPSS/PC) was used.

RESULTS

Patient characteristics and preoperative biochemical variables are shown in table I. The mean age, and fasting blood glucose of patients with diabetes mellitus were significantly greater than values in control patients. There was a delay in the neuromuscular blocking effect of tubocurarine in diabetic patients. This was manifested by an increase in onset of block and zero time (table II). Other variables did not display any significant change. There was a positive correlation between fasting blood glucose concentration and duration of tubocurarine blocking

TABLE I. *Patient characteristics and preoperative biochemical variables (mean (SD)). *Significantly different from control (P < 0.05)*

	Control group	Diabetic group
n	15	25
Sex (M/F)	9/6	14/11
Age (yr)	37.8 (21–60)	52.3 (35–70)*
Body weight (kg)	75.0 (13.5)	71.5 (10.6)
Fasting blood glucose concn (mg dl^{-1})	91.7 (16.2)	129.4 (41.4)*
Serum Na^+ (mg dl^{-1})	140.1 (2.9)	140.6 (2.9)
Serum K^+ (mg dl^{-1})	3.9 (0.5)	3.9 (0.5)
Serum Ca^{2+} (mg dl^{-1})	9.5 (0.5)	9.4 (0.8)
pH	7.39 (0.03)	7.38 (0.04)
P_{CO_2} (kPa)	5.1 (0.3)	5.3 (0.4)

TABLE II. *Neuromuscular variables after administration of tubocurarine 0.25 mg kg^{-1} (mean (SD)). *Significant difference from control (P < 0.05)*

	Control group	Diabetic group
Onset of relaxation (min)	1.6 (0.8)	2.2 (1.0)*
Zero time (min)	1.4 (0.5)	1.7 (0.4)*
Duration of relaxation (min)	39.1 (15.7)	49.9 (25.9)
Recovery time (min)	17.9 (8.3)	14.9 (7.3)
Total dose of tubocurarine (μg kg^{-1} min^{-1})	2.5 (0.9)	2.4 (0.8)
Total dose of neostigmine (μg kg^{-1})	27 (13)	25 (11)

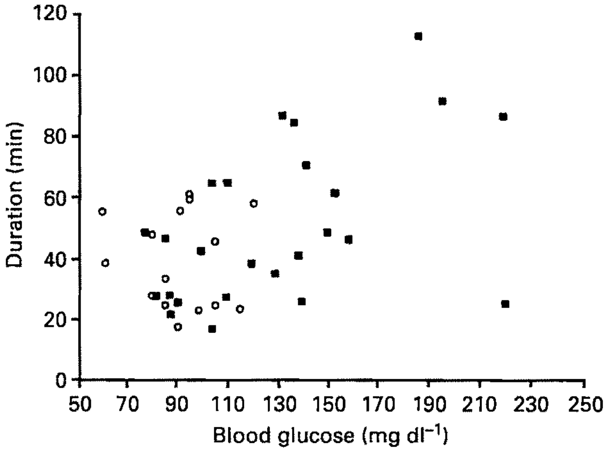

FIG. 1. Plot of fasting blood glucose concentration of diabetic (■) ($n = 25$) and non-diabetic (○) ($n = 15$) patients and the duration of effect of tubocurarine 0.25 mg kg^{-1} calculated from its injection until a twitch height of 10% of the basal value was regained.

TABLE III. *Correlation coefficient* (r) *and multiple regression* (t) *analysis of the no-response time (NRT) against post-tetanic count (PTC), and post-tetanic twitch height percent (PTTH %) in patients with diabetes mellitus and a control group.* * *Significantly different from control* ($P < 0.05$)

	PTC (number)			NRT (mean (SD))		PTTH % (mean (SD))
	Median	Range				
Control group	10	18		16.6 (13.3)		33.5 (21.5)
r	—	—	−0.211	—	−0.897	—
t	—	—	−0.222	—	−4.778	—
Diabetic group	10	25		25.2 (18.1)		26.6 (19.6)
r	—	—	−0.548*	—	−0.296*	—
t	—	—	−2.270*	—	−0.120*	—

effect in diabetic patients ($r = +0.506$, critical value±0.395). This was not present in the control group (fig. 1).

In patients who demonstrated the no-response state following the administration of the initial dose of tubocurarine (table III) NRT correlated negatively ($r = -0.548$, critical value±0.531) with PTC in patients with diabetes mellitus, and with PTTH % ($r = -0.897$, critical value±0.664) in the control group. Multiple regression analysis using the variables PTC and PTTH %, and time as a dependable variable, revealed a significant relationship with PTTH % ($t = -4.778$, $P = 0.003$) in the control group, and with PTC ($t = -2.270$, $P = 0.04$) in diabetes patients.

DISCUSSION

There is considerable variation in the rate of onset of neuromuscular blocking effect of tubocurarine in patients with type II diabetes mellitus. Thickening of the basement membrane of blood capillaries results from deposition of glycoproteins [8] and is present in all tissues including skeletal muscles [9]: this may contribute to this delayed effect. The blood capillary membrane of patients with diabetes mellitus has been found to be less permeable to urea [10].

The mean age of the patients with diabetes mellitus in this study was greater than that of the control group. However, the reported delay in the Tendo-Achilles reflex in diabetes mellitus was not found to correlate with age in another study [3].

There was no significant difference in the dose of tubocurarine administered in the two groups. The reported decrease in sensitivity to tubocurarine in diabetic rats [5] was not confirmed in experimental studies [1, 6].

Previous investigators [11] have attributed tetanic fade to prejunctional cholinoceptor activity, and changes in peak tetanic tension to postjunctional cholinoceptors. In our study, PTC mimics tetanic fade and may represent prejunctional cholinoceptor activity, whilst PTTH % represents peak tetanic tension and may represent postjunctional cholinoceptor activity. During the no-response state, NRT correlated with PTC in diabetic patients and with PTTH % in the control group. Our study suggests that diabetes mellitus reverses the normal relative reactivity of prejunctional and postjunctional cholinoceptors to tubocurarine.

ACKNOWLEDGEMENT

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DEXMEDETOMIDINE REDUCES INTRAOCULAR PRESSURE, INTUBATION RESPONSES AND ANAESTHETIC REQUIREMENTS IN PATIENTS UNDERGOING OPHTHALMIC SURGERY

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SUMMARY

We studied the effects of a single i.v. dose of dexmedetomidine, a highly selective and specific $alpha_2$ adrenoceptor agonist, on intraocular pressure (IOP), haemodynamic and sympathoadrenal responses to laryngoscopy and tracheal intubation, and on anaesthetic requirements in ophthalmic surgery. Thirty ASA I–II patients undergoing cataract surgery were allocated randomly to receive either dexmedetomidine 0.6 $\mu g\ kg^{-1}$ or saline placebo i.v. 10 min before induction of anaesthesia in a double-blind design. After dexmedetomidine there was a 34% (95% confidence interval (CI) 27–43%) reduction in IOP ($P < 0.001$) and 62% (CI 57–68%) decrease in plasma noradrenaline concentrations ($P < 0.001$). After intubation, maximum heart rate was 18% (CI 3–33%, $P = 0.036$) and the maximum IOP 27% (CI 11–43%, $P = 0.005$) less in the dexmedetomidine group compared with the patients treated with placebo. Within 10 min after intubation, maximum systolic and diastolic arterial pressures were also significantly ($P = 0.013$ and $P = 0.020$) smaller in the dexmedetomidine group. The induction dose of thiopentone was smaller (23% (CI 20–26%) $P = 0.012$), and the use of isoflurane or fentanyl supplements during anaesthesia was less frequent in the dexmedetomidine group. The patients premedicated with dexmedetomidine recovered faster from anaesthesia ($P = 0.042$). These results suggest that dexmedetomidine may be a useful anaesthetic adjunct in ophthalmic surgery.

KEY WORDS

Eye: intraocular pressure. Intubation, tracheal: sympathoadrenal response. Sympathetic nervous system: α adrenergic agonist, dexmedetomidine.

The goal of anaesthetic management during ophthalmic surgery is to provide good control of intraocular pressure (IOP), an immobile, uncongested operative field and cardiovascular stability, combined with an adequate level of anaesthesia [1, 2]. In geriatric patients, who frequently have several co-existing diseases, these objectives may often be achieved safely using regional anaesthesia, but in younger patients and in major ophthalmic surgery, general anaesthesia is often considered the method of choice [3–5]. Various pharmacological interventions and anaesthetic techniques have been used to modify the IOP increases and cardiovascular responses after laryngoscopy and tracheal intubation, but none has been entirely successful [1, 2, 4–6].

Clonidine, a centrally acting $alpha_2$ adrenoceptor agonist and antihypertensive agent, reduces anaesthetic requirements, improves perioperative haemodynamic and adrenergic stability and reduces IOP [7–9]. Dexmedetomidine is the pharmacologically active D-isomer of medetomidine, a highly selective, specific and potent $alpha_2$ adrenoceptor agonist [10]. Medetomidine has a considerably higher $alpha_2$:$alpha_1$ selectivity ratio than clonidine in receptor binding experiments and, compared with clonidine, dexmedetomidine may have more efficacy at $alpha_2$ adrenoceptors [10, 11].

Dexmedetomidine has potent hypnotic–anaesthetic actions in rats, mediated via central $alpha_2$ adrenoceptors [12]. In recent studies, i.v. dexmedetomidine was shown to reduce the requirements for thiopentone and isoflurane during gynaecological surgery [13, 14]. In addition, it decreased both normal and increased IOP in studies with awake rabbits [15]. Therefore, we designed a double-blind, placebo-controlled study to evaluate the effects of dexmedetomidine on IOP and sympathoadrenal and cardiovascular responses to laryngoscopy and tracheal intubation, and its influence on anaesthetic requirements during ophthalmic surgery.

PATIENTS AND METHODS

We studied 30 ASA I–II patients of both sexes, aged 65 yr or less (range 18–65 yr), undergoing surgical cataract extraction (table I). All gave written informed consent. Patients with cardiovascular medications likely to affect the response to the trial medication were excluded. The study was approved

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by the Ethics Committee of Turku University Hospital and the Finnish National Board of Health was informed.

Design of the study

The trial was a placebo-controlled phase II study. The patients were allocated randomly (balanced randomization using a computer program, block size 10) to receive either dexmedetomidine 0.6 $\mu g\ kg^{-1}$ (0.06 ml kg^{-1}) ($n = 15$) or an equal volume of saline ($n = 15$) i.v. in 1 min 10 min before induction of anaesthesia. The dose of dexmedetomidine was based on the results of the previous phase II studies [13]. The study was conducted in a double-blind fashion. The coded ampoules were supplied by Orion Corporation Farmos, R&D Pharmaceuticals, Turku, Finland.

The patients entered the hospital 1 or 2 days before the scheduled surgery. Routine clinical chemistry tests, ECG and chest x-ray were performed. All patients received oral diazepam 5 mg 90 min before surgery, which was performed between 08:00 and 12:00. After the arrival of the patient in the operating unit, ECG and heart rate (Olli Monitor 431 D, Kone Corporation, Espoo, Finland) were monitored continuously and non-invasive recording of systolic and diastolic arterial pressures at 5-min intervals were started with an automated oscillometric device (Sphygmomanometer 103 N, Nippon Colin, Tokyo, Japan). A vein in the right antecubital fossa was cannulated for blood sampling, and a second cannula was inserted into the dorsum of the left hand for i.v. infusion (2.5% glucose in 0.45% saline, 6–8 ml $kg^{-1}\ h^{-1}$) and administration of drugs.

Anaesthetic management

Before induction of anaesthesia, glycopyrronium 4 $\mu g\ kg^{-1}$ and fentanyl 2 $\mu g\ kg^{-1}$ were administered i.v.

Patients were preoxygenated with 100% oxygen via a facemask (oxygen flow 9 litre min^{-1}). The induction dose of thiopentone was defined as described by Dundee and colleagues [16]: thiopentone 1.5–2 mg kg^{-1} (to the nearest 25 mg) was injected within 10 s and further increments of 25–50 mg at 15-s intervals were given i.v. until disappearance of the eyelash reflex. The patient's lungs were then ventilated manually with 100% oxygen. Pancuronium 0.1 mg kg^{-1} was administered to produce neuromuscular block, which was monitored with a peripheral neurostimulator (Innervator NS 252, Fisher & Paykel Electronics Ltd, Auckland, New Zealand). After disappearance of the twitch response, the duration of laryngoscopy was standardized at 10 s from the moment the vocal cords were seen before tracheal intubation. After intubation, mechanical ventilation of the lungs (Servo 900 B, Siemens Elema, Solna, Sweden) was started and anaesthesia was maintained with 70% nitrous oxide in oxygen. Fentanyl 1 $\mu g\ kg^{-1}$ and isoflurane were administered according to the predetermined criteria (see below). Ventilation was adjusted to maintain the end-tidal $P\text{CO}_2$ at 4.5–5.5 kPa (Cardiocap, Datex Instrumentarium Corporation, Helsinki, Finland). For further neuromuscular block, additional doses of pancuronium 1–2 mg were given according to the train-of-four response.

Anaesthetic management was designed to maintain arterial pressure and heart rate within 20% limits of the preoperative values and within clinically acceptable limits (systolic arterial pressure greater than 80 mm Hg and less than 180 mm Hg). Preoperative values were defined as the mean of the recordings made on the previous day and immediately before the trial medication.

Hypertension and tachycardia were treated primarily by deepening anaesthesia with 1-$\mu g\ kg^{-1}$ doses of fentanyl i.v. or with isoflurane in 0.5% increments in the inhaled concentration. Hypotension (reduction in arterial pressure of 20% or more from the baseline) was treated primarily by increasing the i.v. infusion rate, by reducing isoflurane concentration, and with 3-mg bolus doses of etilefrine, a direct alpha_1 sympathomimetic agent. For bradycardia, defined as heart rate less than 45 beat min^{-1}, i.v. glycopyrronium 0.2 mg was readily available. Isoflurane administration was terminated about 10 min before the end of surgery and nitrous oxide administration was terminated at the moment when neuromuscular block was antagonized with glycopyrronium 10 $\mu g\ kg^{-1}$ and neostigmine 50 $\mu g\ kg^{-1}$.

After operation, patients were monitored in the recovery room until there were no signs of drug-induced adverse effects (e.g. excessive tiredness, hypotension, postoperative restlessness), but at least for 3 h. For postoperative pain control, oxycodone was administered in incremental doses of 3 mg i.v.

Clinical assessments

Arterial pressure and heart rate were recorded 15 and 1 min before administration of the test drug, 5 and 1 min before induction, at 2-min intervals until 10 min after induction, at 5-min intervals during the rest of the surgery and at 15-min intervals in the recovery room. ECG monitoring was continued throughout the study.

After topical application of local anaesthetic (0.4% oxybuprocaine hydrochloride) IOP was measured with a Schiötz tonometer 2 min before premedication, 2 min before induction, 1 min after induction and 1, 2 and 5 min after intubation. All measurements were performed on the eye which was not to be operated. The average value of three readings was recorded at each time.

The induction dose of thiopentone, the concentration and the administration time of isoflurane, the total amount of fentanyl needed during operation and the eventual need for etilefrine or other medications were recorded. The number of interventions needed during anaesthesia, the time between the termination of nitrous oxide inhalation and the recovery of consciousness (response to a verbal command) was recorded, as was the amount of oxycodone needed in the recovery room.

Biochemical measurements

Blood samples were collected 1 min before administration of the test drug, 1 min before induction, 1 min after induction and 1 min after intubation for the measurement of plasma concentrations of noradrenaline, 3,4-dihydroxyphenylglycol (DHPG) and adrenaline in plasma. The blood was collected into chilled polypropylene tubes with K_2EDTA, which were stored in ice until centrifuged within 2 h at 0–4 °C. The plasma samples were stored at −70 °C until required for assay. The concentrations of noradrenaline, DHPG and adrenaline in the plasma were measured using high pressure liquid chromatography with coulometric electrochemical detection [17, 18].

The reproducibility of the assay was tested using pooled plasma samples from previous clinical studies, and the resulting intra-assay coefficients of variation (CV) were less than 2 % for noradrenaline, about 4 % for DHPG and approximately 10 % for adrenaline in the relevant concentration ranges. All the samples from one experimental session were analysed in the same batch.

Statistical analysis

Patient characteristics and baseline data were compared with Student's *t* test or Fisher's exact test. Analysis of variance (ANOVA) for repeated measurements with one between-factor (drug) and one within-factor (time) was used for IOP and plasma catecholamine data. Greenhouse–Geisser adjusted *P* values are reported in cases of violation of the sphericity assumption. In a case of a significant drug × time interaction in ANOVA, the analysis was continued by calculating contrasts for the clinically most relevant comparisons. The maxima and minima of the cardiovascular variables and IOP were compared with Student's *t* test. The number of patients needing etilefrine, additional fentanyl and isoflurane was compared with Fisher's exact test; all other data concerning anaesthetic requirements were tested with Student's *t* test, or in case of non-normal distributions, with the Mann–Whitney *U* test.

Results are expressed as mean (SEM) or as median (range); 95 % confidence intervals (CI) were calculated for the main end points. $P < 0.05$ was considered statistically significant.

All statistical work was undertaken at Orion Corporation Farmos, R&D Pharmaceuticals, using BMDP and SAS softwares in a VAX 3100 computer with the VMS operating system.

RESULTS

The patient groups were comparable in gender distribution, age, body weight and resting values of arterial pressure, heart rate and IOP (table I). Dexmedetomidine was well tolerated and no serious drug-related side-effects were recorded. Hypotension (decrease of more than 20 % of baseline) during surgery was treated with etilefrine in four subjects, three in the dexmedetomidine group ($P = 0.60$, Fisher's exact test). None of the patients needed additional treatment for bradycardia, defined as a heart rate less than 45 beat min^{-1}. No ECG abnormalities were observed. The median (range) duration of surgery was 49 min (21–80 min) in the dexmedetomidine group compared with 66 min (26–128 min) in the placebo group ($P = 0.062$, Mann–Whitney *U* test).

Heart rate and arterial pressure

The increase in heart rate associated with laryngoscopy and tracheal intubation was attenuated

TABLE I. *Patient characteristics (mean* (SEM) *[range]). Dex. = Dexmedetomidine. No statistically significant differences between groups*

	Placebo	Dex.
Age (yr)	48 [18–65]	47 [28–62]
Weight (kg)	77 (4) [53–115]	78 (4) [51–100]
Height (cm)	171 (3) [150–191]	172 (3) [156–186]
Sex (M:F)	8:7	9:6
Preoperative		
IOP (mm Hg)	13 (1) [8–17]	14 (1) [8–19]
HR (beat min^{-1})	71 (2) [58–81]	71 (2) [58–84]
SAP (mm Hg)	131 (5) [95–165]	132 (4) [100–165]
DAP (mm Hg)	79 (3) [60–90]	81 (3) [60–100]

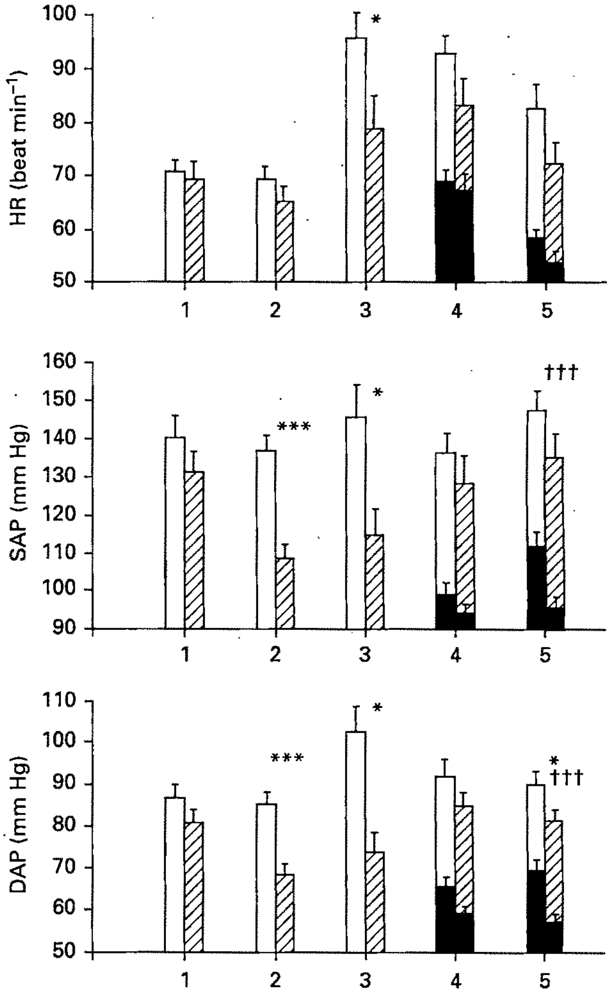

FIG. 1. Heart rate (HR), systolic (SAP) and diastolic (DAP) arterial pressure (mean (SEM) at baseline (1), at induction (2) and means (SEM) of individual maxima and minima (black columns) over time after intubation (3), during operation (4) and in the recovery ward (5)). □ = Placebo group; ▨ = dexmedetomidine group. *$P < 0.05$; ***$P < 0.001$ between groups. †††$P < 0.001$ compared with minima.

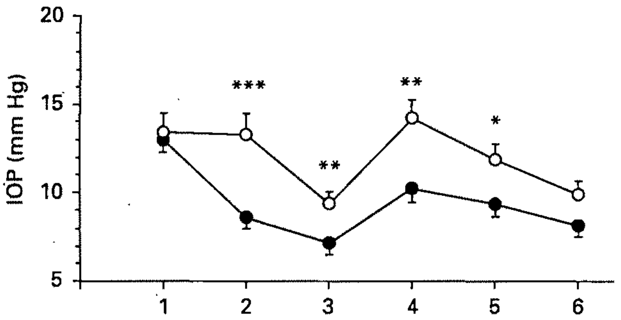

FIG. 2. Mean (SEM) intraocular pressure (IOP) before premedication (1), 2 min before induction (2), 1 min after induction (3) and 1 min (4), 2 min (5) and 5 min (6) after intubation. $*P < 0.05$; $**P < 0.01$; $***P < 0.001$ between placebo (○) and dexmedetomidine (●) groups.

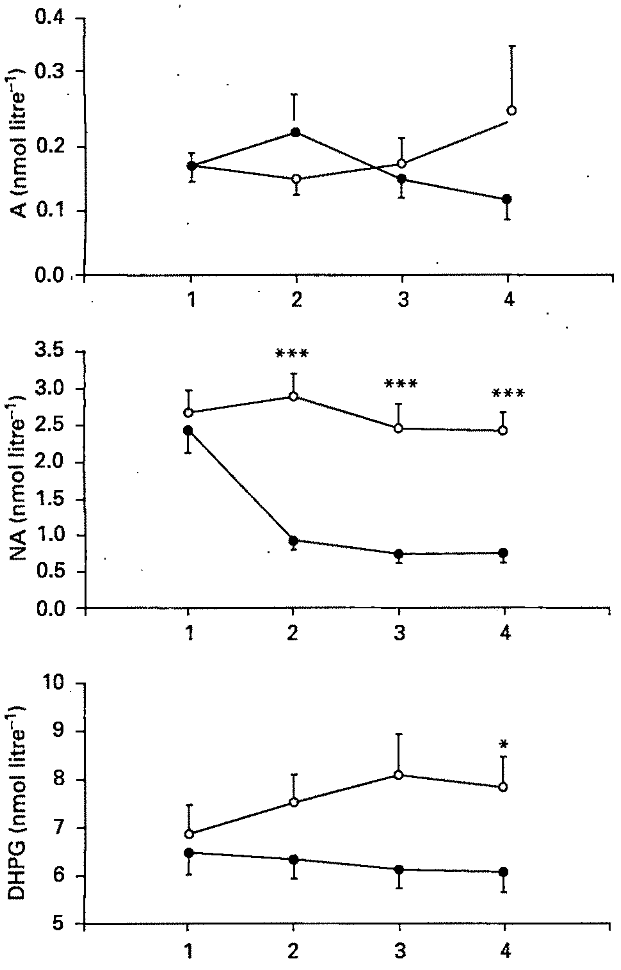

FIG. 3. Mean (SEM) plasma catecholamine concentrations before premedication (1), 1 min before induction (2), 1 min after induction (3) and 1 min after intubation (4). NA = Noradrenaline; A = adrenaline. $*P < 0.05$; $***P < 0.001$ between placebo (○) and dexmedetomidine (●) groups.

significantly by dexmedetomidine compared with placebo ($P = 0.036$, t test). The maximum heart rate after intubation was 18% (CI 3–33%) less in the dexmedetomidine group (79 (SEM 6) beat min^{-1}) than in the placebo group (95 (5) beat min^{-1}) (fig. 1).

Dexmedetomidine induced relatively modest, but statistically significant decreases in systolic and diastolic arterial pressures at the time of induction ($P < 0.001$ for both, t test). The systolic and diastolic pressure maxima within 10 min after intubation also were smaller in the dexmedetomidine group ($P = 0.013$ and $P = 0.020$, t test) (fig. 1). The minimum and maximum pressure values during the operation were not significantly different between the groups. Patients in the dexmedetomidine group had smaller minimum ($P < 0.001$, t test) and maximum ($P = 0.038$, t test) diastolic and minimum systolic ($P < 0.001$, t test) arterial pressures in the postoperative period compared with those in the saline group (fig. 1).

Intraocular pressure

Dexmedetomidine induced a statistically significant decrease in IOP ($P = 0.013$, drug × time interaction in ANOVA) (fig. 2). Before induction, the decrease in IOP in the dexmedetomidine group was 34% (CI 27–43%) compared with the placebo group ($P < 0.001$, ANOVA). After intubation, the maximum IOP was 27% (CI 11–43%) smaller in the dexmedetomidine group than in the patients treated with placebo ($P = 0.005$, t test). Five minutes after intubation, the IOP were no longer significantly different between groups ($P = 0.077$, ANOVA).

Plasma catecholamine concentrations

Plasma concentrations of noradrenaline and one of its main metabolites, DHPG, measured as indicators of sympathetic nervous system activity, decreased significantly after administration of dexmedetomidine ($P < 0.001$ for both variables for drug × time interaction in ANOVA) (fig. 3). The plasma concentration of noradrenaline was decreased by 62% (CI 57–68%) before induction of anaesthesia. Induction of anaesthesia was associated with a small decrease in plasma noradrenaline concentration in both groups compared with preinduction values (fig. 3). Laryngoscopy and tracheal intubation did not cause any further increase in plasma catecholamine concentration, but plasma noradrenaline concentration remained smaller in the dexmedetomidine group, being only 31% of the noradrenaline concentration after placebo. The concentrations of adrenaline in plasma were low, and not significantly different between groups.

Anaesthetic requirements

The induction dose of thiopentone was significantly smaller (23%; CI 20–26%) in the dexmedetomidine group ($P = 0.012$, t test). In order to maintain heart rate and arterial pressure within the predetermined limits, additional supplements of isoflurane, fentanyl, or both, were needed more often in the saline group (table II). Isoflurane was used more often ($P = 0.037$, Fisher's exact test) in the placebo group. Although more fentanyl was administered in the placebo group, the difference was not statistically significant. Six patients (40%) in the placebo group needed both fentanyl and isoflurane, while in the dexmedetomidine group only one patient (7%) was treated with both agents ($P = 0.08$, Fisher's exact test).

Anaesthetic requirements are summarized in table II. The recovery time (response to verbal command after termination of nitrous oxide administration)

TABLE II. *Anaesthetic requirements (mean (SEM) or median (range))*

	Placebo ($n = 15$)	Dex. ($n = 15$)	P
Induction dose of thiopentone (mg)	315 (21)	242 (17)	0.012
Additional fentanyl (No. of patients)	8	3	0.128
Isoflurane administered (No. of patients)	10	4	0.037
Both fentanyl and isoflurane administered (No. of patients)	6	1	0.080
Duration of isoflurane administration (min)	17 (0–94)	0 (0–82)	0.018
Inspiratory isoflurane concentration (vol %)	0.20 (0–0.75)	0.0 (0–0.54)	0.031
Interventions during anaesthesia (No.)	3 (0–6)	0 (0–7)	0.040

was shorter in the dexmedetomidine group (118 (10) s) compared with placebo (156 (15) s) ($P = 0.042$, t test). After operation, two dexmedetomidine patients and one in the placebo group needed oxycodone in the recovery room.

DISCUSSION

We have found that a single i.v. dose of dexmedetomidine 0.6 $\mu g\ kg^{-1}$ effectively attenuated the increase in heart rate associated with laryngoscopy and tracheal intubation observed in the control group. Systolic and diastolic arterial pressures were also significantly less in the dexmedetomidine group. In addition, attenuated sympathetic activity was accompanied by decreases in plasma concentrations of noradrenaline (60–70 %) and one of its main metabolites, DHPG. Excessive bradycardia requiring treatment was not observed, not even in connection with the traction of extraocular muscles during surgery, the most common stimulus for the oculo–cardiac reflex [1]. However, all patients received glycopyrronium 4 $\mu g\ kg^{-1}$ and pancuronium, which has vagolytic effects.

Intraocular pressure

IOP is determined by extraocular muscle tone, scleral rigidity, vascularity of the orbit and production and outflow of aqueous humor [2, 4]. Dexmedetomidine prevented almost entirely the increase in IOP after laryngoscopy and tracheal intubation. The decrease in IOP was 34 % after dexmedetomidine even before the adminstration of any other medication. After induction of anaesthesia with thiopentone, IOP decreased significantly in the placebo group also, but it returned to baseline values after laryngoscopy and tracheal intubation. The reduction in IOP induced by systemic administration of dexmedetomidine was of the same magnitude as that reported in a previous study with clonidine [9].

Thiopentone reduces IOP mainly via its depressant effect on the central diencephalic controlling areas for IOP, although increased aqueous drainage has also been shown to occur [2, 4]. Studies on the non-depolarizing neuromuscular blocking drug, pancuronium, have revealed either no effect or a decrease in IOP [2, 4]. Fentanyl is also known to reduce IOP [4]. The effect of nitrous oxide on IOP has received little attention [2], but it has been well established that all the volatile inhalation agents decrease IOP in a dose-dependent manner [2, 4]. Several mechanisms of action to alter IOP have been suggested: effects on the central controlling areas in the midbrain, by altering aqueous outflow and by altering extraocular muscle tone [2]. However, these inhalation agents may cause excessive cardiovascular depression, particularly in elderly patients, if concentrations are increased in an attempt to improve the ocular conditions for surgery.

Special attention was paid to intubation conditions during this study, so that the patients were fully paralysed (assessed by peripheral neurostimulator) before tracheal intubation, which was performed after standardized laryngoscopy (10 s). The intubation-induced increase in IOP was transient. Five minutes after intubation, there was no statistically significant difference between the groups.

Anaesthetic requirements

Clonidine has been shown to reduce the requirements for inhalation anaesthetics and opioids during coronary bypass surgery, in ophthalmic and gynaecological surgery [7, 9, 19]. This may be partly a result of analgesic properties, which have been verified after intrathecal, extradural and systemic administration [20, 21]. Dexmedetomidine has been shown to produce dose-dependent analgesia in animals [22], and its analgesic efficacy has recently been demonstrated in humans [23]. Dexmedetomidine has reduced the requirements for thiopentone and isoflurane in gynaecological surgery [13, 14]. Its hypnotic–anaesthetic action in the central nervous system appears to involve an inhibitory signal transduction protein, G_i-protein, which mediates the effect via increased conductance through a hyperpolarizing neuronal potassium channel [24].

In this study, the induction dose of thiopentone was also decreased significantly by dexmedetomidine, and the use of additional isoflurane and fentanyl supplementation for maintenance of anaesthesia was reduced in the dexmedetomidine group.

Sedation produced by dexmedetomidine after administration might have unblinded the clinician administering the anaesthetic agents. However, this probably did not affect the results, because the anaesthetic management was based on strict predetermined haemodynamic and clinical criteria.

In conclusion, we have shown that dexmedetomidine reduced IOP and attenuated the sympatho-adrenal responses associated with laryngoscopy and intubation. It also reduced the requirements for thiopentone, opioid and inhalation anaesthetic agents. More extensive studies in elderly patients and in patients with increased IOP are warranted, to assess its value in routine management of ophthalmic anaesthesia.

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I.V. FLUIDS AND MINOR GYNAECOLOGICAL SURGERY: EFFECT ON RECOVERY FROM ANAESTHESIA†

L. G. OOI, D. R. GOLDHILL, A. GRIFFITHS AND C. SMITH

SUMMARY

This study has examined the effect of hydration on immediate recovery from anaesthesia in two groups of 15 patients undergoing therapeutic abortion. A standard anaesthetic technique was administered. Patients in group I received no preoperative fluid; those in group II received, before anaesthesia, 20 ml kg^{-1} of 4% glucose and 0.18% saline. Recovery was assessed using two tests of psychomotor function: a reaction time test and a letter cancellation task. Subjective symptoms were assessed with a questionnaire. There was a significant decrease in reaction time after operation (both motor and reaction times) in group I (no fluids), but not in group II (fluids). There were no significant between-group differences in objective tests or subjective measures. Thus we could not demonstrate any obvious benefit of i.v. fluid administration. Approximately 500 patients would be required to have an 80% chance of establishing a statistically significant between group difference.

KEY WORDS

Anaesthetic techniques: inhalation. Anaesthetics, intravenous: propofol. Recovery. Fluid balance.

Morbidity after day-stay surgery includes minor, but nonetheless disturbing, complaints of headache, nausea, dizziness and drowsiness [1, 2]. It is common practice for day-stay patients, even those having operations in the afternoon, to be starved from the previous evening, and both dehydration and hypoglycaemia may contribute towards morbidity. Keane and Murray [3] and Spencer [4], showed that i.v. fluid replacement therapy in patients undergoing minor surgery significantly improved recovery. However, their assessments of recovery were subjective, based on questionnaires completed 6 h or more after the anaesthetic. In our study we have also used objective testing to examine the effect of i.v. fluids on immediate recovery from anaesthesia. A control group was compared with a group who received i.v. fluids. Two tests of psychomotor function, a reaction time test and a letter cancellation task, were used to obtain a measure of recovery.

PATIENTS AND METHODS

After Ethics Committee approval and informed written consent were obtained, we studied 30 women undergoing therapeutic abortion as day cases. All patients were of 14 weeks gestation or less, physical status ASA I or II and aged 18–39 yr.

Each patient was given a questionnaire on which she was asked to record on a four-point scale (1 = none; 2 = slight; 3 = moderate; 4 = severe) any symptoms of anxiety, pain, drowsiness, nausea, headache, dizziness, thirst, sore throat, weakness and muscle ache. A 16-gauge i.v. cannula was placed in the non-dominant arm and blood samples were obtained for measurement of blood glucose concentration and plasma osmolality. Each patient was asked also to produce a urine specimen for measurement of urine osmolality.

Psychomotor testing consisted of a four-choice, computer-controlled visual reaction time test and a letter cancellation task. In the former, the patient was presented with a box containing four light emitting diodes (LED), each adjacent to a button. The LED were activated by a computer in a random order at intervals of 50–999 ms. When an LED was illuminated, the patient had to release a start button and press an appropriate button adjacent to the LED in order to extinguish the light. She was instructed to do this as quickly and as accurately as possible. This test measured two basic functions: cognition, which is the time taken to release the start button when the bulb illuminated (reaction time) and motor function, which is the time taken for movement from the start button to the button by the LED (motor time). To familiarize the patient with the test, a practice run of 12 trials was carried out, followed by two blocks of 40 trials. The first five trials in each block were ignored and mean reaction and motor time were calculated using the remaining 70 trials. In the letter cancellation task, the patient was presented with a text containing 140 of the letters *b*, *d* and *e* and asked to delete as many as possible in 150 s. The task was scored according to the number deleted and the number missed. This test measures perceptual speed and accuracy.

Each patient was then allocated randomly to one of two groups. Patients in group I received no fluid and

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those in group II were given 20 ml kg^{-1} of 4% glucose and 0.18% saline over approximately 25 min. No premedication was prescribed. A standard anaesthetic technique was used consisting of induction with propofol 2 mg kg^{-1} and fentanyl 1 μg kg^{-1} and maintenance with 66% nitrous oxide in oxygen, with 20-mg increments of propofol as indicated clinically. The patient breathed spontaneously via a Bain system and each received syntocinon 10 u. i.v. The duration of anaesthesia was taken as the time from induction to discontinuing nitrous oxide.

After operation, the times were recorded for the patient to open her eyes spontaneously, and to obey commands to squeeze a hand and give her correct date of birth. Psychomotor testing and biochemical measurements were repeated 45 min after recovery, the end-point for recovery being when the patient was able to give her correct date of birth. All testing was carried out by an observer who was blinded to group allocation. Patients were asked also to complete a questionnaire of subjective side effects.

Patient data were analysed using independent t tests between the two groups. Biochemical results, motor and reaction times and letter cancellation scores were analysed using one-way analysis of variance between the four groups (group I preop.; group I postop.; group II preop.; group II postop.), and individual comparisons were made using the Student–Newman–Keuls test. Within-groups statistical significance was analysed using paired t tests. Statistical significance was taken as $P < 0.05$.

RESULTS

One patient from group II was excluded because she did not co-operate with psychomotor testing.

There were no differences between the two groups in age, weight, duration of anaesthesia and total dose of anaesthetic drugs used (table I). The duration of starvation averaged approximately 10 h in both groups (table I).

Times to spontaneous eye opening, obeying commands and giving the correct date of birth were comparable between the two groups (table II).

In group I (no fluids), there were no significant differences between preoperative and postoperative values for blood glucose concentration and plasma and urine osmolalities (table III). Compared with values before operation, blood glucose concentration after operation in group II was significantly increased, while the postoperative urine osmolality was significantly less. These values were also significantly increased and reduced, respectively, compared with corresponding values in group I.

Within group I (no fluids), postoperative reaction and motor times were prolonged significantly compared with preoperative values (table IV). Within group II, although there was a trend for postoperative reaction and motor times to be longer than those before operation, this difference was not statistically significant. When reaction and motor times in group I were compared with reaction and motor times in group II, there were no statistically significant differences. With the letter cancellation task, there were no significant differences in the scores within the groups or between the groups.

There were no obvious differences between the groups in subjective assessments of side effects (fig. 1). Compared with preoperative assessment, after

TABLE I. *Patient data (mean (range or SEM))*

	Group I (no fluid) ($n = 15$)	Group II (fluid) ($n = 15$)
Age (yr)	24.5 (18–33)	27.2 (18–39)
Weight (kg)	62.4 (2.0)	60.8 (2.3)
Gestation (week)	9.58 (0.34)	9.02 (0.47)
Last oral intake (h)	10.0 (0.75)	10.4 (0.9)
Duration of anaesthesia (min)	7.0 (0.2)	6.5 (0.2)
Total dose of propofol (mg)	199.3 (4.1)	199.3 (6.5)
Total dose of fentanyl (μg)	57.3 (1.8)	57.1 (2.1)

TABLE II. *Initial measures of recovery (mean (SEM))*

Time to (min)	Group I (no fluid) ($n = 15$)	Group II (fluid) ($n = 15$)
Eye opening	5.48 (0.87)	5.27 (0.27)
Obeying commands	6.06 (0.24)	5.95 (0.30)
Giving correct date of birth	6.62 (0.21)	6.36 (0.26)

TABLE III. *Biochemical results (mean (SEM)). *P < 0.05 compared with group II before operation and with group I before and after operation*

	Group I (no fluid) ($n = 15$)	Group II (fluid) ($n = 15$)
Glucose (mmol $litre^{-1}$)		
Before op.	4.1 (0.2)	4.2 (0.1)
After op.	4.4 (0.1)	5.3 (0.1)*
Plasma osmolality (mosmol $litre^{-1}$)		
Before op.	274 (2.6)	277 (5.9)
After op.	272 (1.7)	266 (2.2)
Urine osmolality (mosmol $litre^{-1}$)		
Before op.	769 (66.1)	801 (45.3)
After op.	817 (64.5)	475 (97.3)*

TABLE IV. *Results of psychomotor testing (mean (SEM)). *P < 0.05 compared with group I before operation*

	Group I (no fluid) ($n = 15$)	Group II (fluid) ($n = 14$)
Reaction time (ms)		
Before op.	333.6 (14.9)	350.1 (17.3)
After op.	373.0 (20.5)*	380.7 (31.5)
Motor time (ms)		
Before op.	209.4 (11.9)	195.3 (11.3)
After op.	234.5 (13.9)*	210.8 (17.7)
Deletion score		
Before op.	95.4 (3.8)	102.1 (1.6)
After op.	95.1 (2.8)	101.7 (0.9)

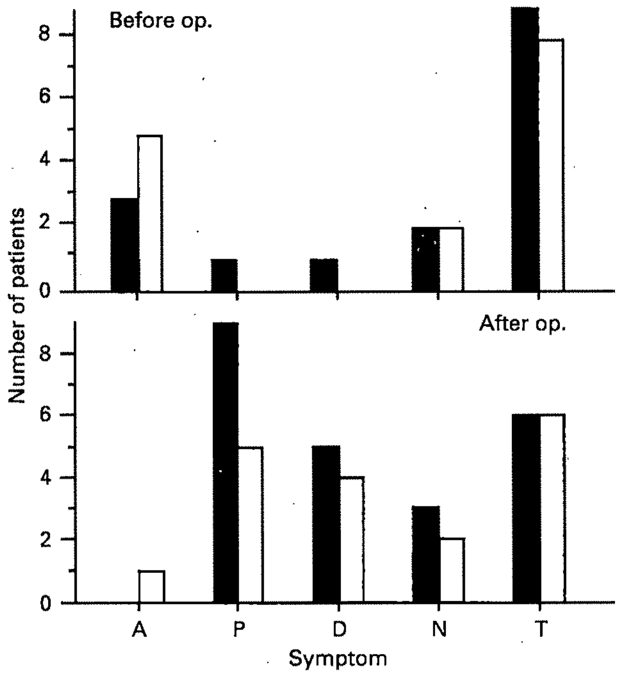

FIG. 1. Number of patients with moderate or severe subjective symptoms. ■ = Group I (no fluid); □ = group II (fluid). A = Anxiety; P = pain; D = drowsiness; N = nausea; T = thirst.

the anaesthetic there were fewer patients with moderate or severe anxiety, and more with moderate or severe pain or drowsiness. Most patients felt thirsty before the operation and there was no difference between the groups at postoperative assessment in subjective assessment of thirst. There were also no differences between the groups in both pre- and postoperative complaints of muscle aches, dizziness, weakness, sore throat or headaches.

DISCUSSION

Although it is not routine practice in the U.K. to administer i.v. fluids to patients undergoing minor surgery, this is common in other countries, including the United States [5]. There is a high incidence of minor morbidity after short surgical procedures under general anaesthesia [1, 2] and two studies [3, 4] have shown that giving patients i.v. fluids resulted in a clinically significant reduced incidence of postoperative nausea, dizziness, drowsiness, thirst and headache. The exact mechanism is unclear, but dehydration may be an important contributory factor, as most patients presenting for day-case surgery have been starved for at least 10 h and depletion of both extracellular and intracellular fluid volumes may cause symptoms of nausea, dizziness and drowsiness. Hypoglycaemia has been implicated also in the occurrence of postoperative morbidity and a recent study [6] which investigated the effect of a fluid and calorie load found a significant improvement in postoperative outcome in those who received i.v. glucose.

Measurement of plasma and urine osmolality and plasma glucose concentration demonstrated that the i.v. fluid our patients received had a measurable effect. Although our study concentrated on psychomotor recovery in the immediate postoperative period it is worth noting that postoperative symptoms were similar in both groups. Psychomotor function was assessed using the four-choice visual reaction time test and the letter cancellation task. These two tests measured perceptual speed and accuracy, concentration, reaction and motor times, and have been shown to be sensitive tests of recovery after anaesthesia [7]. However, we found no differences within or between the groups in the letter cancellation scores and this test was unable to detect effects of anaesthesia. The four-choice reaction and motor time tests were sensitive enough to distinguish between preoperative and postoperative values in control patients, but not in those who received i.v. fluid. There was no significant difference between the postoperative motor or reaction times of the two groups. This may be because the limited number of patients studied failed to reveal subtle differences between the groups. Power analysis of the data estimates that, in order to have an 80% chance of finding a significant ($P < 0.05$) difference between the groups, a study of about 500 patients would be required. This approach gives an indication of differences on a group basis. However, it has been pointed out that group analysis may mask impairment in individuals which may be clinically important [8]. Indeed, there was considerable variation in reaction time after operation in both groups. One way to approach this in future studies would be to assess a large bank of controls and express scores of treated subjects in confidence interval units.

On the basis of this study, it cannot be concluded that administration of i.v. fluids before operation has a beneficial effect on recovery from minor surgical procedures. Factors other than hydration influence recovery and overall well-being and these include the nature and duration of the procedure, the anaesthetic technique used and the reaction of the individual patient. Our patients were healthy, experienced little postoperative pain and underwent surgery of very short duration (mean anaesthetic time 6.8 min). The emotional overlay of the therapeutic abortion may also affect the results of the tests and the subjective assessment of recovery. The anaesthetic was tailored to suit the procedure. Propofol is recognized to be associated with an excellent quality of recovery and a low incidence of postoperative morbidity [9]. Our patients were awake soon after the procedure, and were able to eat and drink and be discharged within 2 h of awakening. We would therefore be circumspect about extending our conclusions to other procedures and anaesthetic techniques from which immediate recovery is not as good.

Where i.v. fluids are administered routinely to day-case patients, considerable cost saving could be achieved if this practice were to cease. Our study shows that patients may be starved for a long period before minor surgery. Clear fluids are absorbed rapidly from the stomach and, before elective procedures, it is safe for patients to drink up to 150 ml 2–3 h before operation [10]. Although we found no measurable benefit from i.v. fluids, if perioperative dehydration is a concern, then oral fluids may be beneficial without the expense of i.v. administration.

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CONTINUOUS EXTRADURAL ANALGESIA: COMPARISON OF MIDWIFE TOP-UPS, CONTINUOUS INFUSIONS AND PATIENT CONTROLLED ADMINISTRATION

J. PURDIE, J. REID, J. THORBURN AND A. J. ASBURY

SUMMARY

We have compared three techniques used to provide extradural analgesia during the first stage of labour: 0.25% plain bupivacaine 10 ml demand top-ups delivered by the midwife; continuous infusion of 0.125% plain bupivacaine 10 ml h^{-1}; and patient-controlled extradural analgesia (PCEA) delivering 3-ml boluses of 0.25% bupivacaine. Each technique produced comparable analgesia achieving equivalent maternal satisfaction, with no difference in mode of delivery and no complications. This regimen for PCEA proved a viable alternative for continuous extradural analgesia and was popular with the mothers, midwives and anaesthetists.

KEY WORDS

Anaesthesia, extradural: patient-controlled. Anaesthesia: obstetric. Anaesthetics, local: bupivacaine.

Continuous extradural analgesia is accepted as the most effective method of providing good pain relief in labour. In addition to conventional top-up regimens, extradural analgesia may be provided by continuous infusions; the advantages and disadvantages of these two techniques are well recognized.

Several recent studies have demonstrated the efficacy of patient-controlled extradural analgesia (PCEA) in labour [1–3]. To achieve adequate analgesia, top-ups are required more frequently, but the timing of these is under the patient's own control.

The aim of this study was to compare the analgesia provided by three methods of continuous extradural analgesia, including PCEA, in a labour suite where midwife administration of top-ups of 0.25% bupivacaine has been practised routinely for many years.

PATIENTS AND METHODS

After hospital Ethics Committee approval and informed consent, we studied 300 women requiring extradural analgesia in labour. An extradural block was established at L2–3 or L3–4 with 0.25% bupivacaine 10 ml. When pain free contractions were experienced, the extent of the sensory block was assessed. Patients were then allocated randomly to receive continuous analgesia by one of three methods:

Midwife top-ups (*MWT*). Top-up injections of 0.25% bupivacaine 3 ml initially followed, 5 min later, by 7 ml, administered by the sister midwife. This technique has been routine practice in our unit for many years.

Infusion group. Continuous infusion of 0.125% bupivacaine 10 ml h^{-1}.

PCEA group. Graseby patient-controlled analgesia pump from which they were allowed to demand an hourly maximum of four 3-ml boluses with a 5-min lockout interval.

The attending midwife monitored maternal heart rate and systolic arterial pressure at 5-min intervals after top-ups and thereafter every 30 min. The level of T7 was marked by adhesive tape on the anterior abdominal wall and the extent of the sensory loss was assessed every 1 h, using ice. The anaesthetist was informed if sensory loss extended above T7, and in the case of the infusion group the rate was reduced or stopped accordingly. If analgesia was inadequate, the anaesthetist was called and supplementary extradural injections, partial withdrawal of catheter in the extradural space or resiting of the extradural catheter were defined as anaesthetist interventions.

The obstetric management of each group was uniform until full cervical dilatation was achieved. Consequently, analysis of analgesia is confined principally to the first stage of labour. Pain was assessed as follows.

Quality of analgesia was assessed by the attending midwife: 0 = no pain, pressure or tightening; 1 = aware of tightening or pressure, but not painful; 2 = slight pain or pressure, but not distressing; 3 = distressing pain or pressure. These assessments were performed at 1-h intervals. The number of recordings of each score was summed from all women in

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TABLE I. *Patient characteristics (mean (range or* SD*)), type (No. (%)) and duration (mean* (SD)) *of labour, and mode of delivery (No. (%)). MWT = Midwife top-up; PCEA = patient-controlled extradural analgesia; Infusion = continuous infusion; SVD = spontaneous vertex delivery; LCFD = low cavity forcep delivery; MCFD = mid cavity forcep delivery; KRFD = Kiellands rotation forcep delivery; Vent. = ventouse extraction delivery; MR/FD = manual rotation plus forcep delivery; EmLUSCS, Ext. = emergency lower uterine segment Caesarean section under extradural anaesthesia; EmLUSCS, GA = emergency lower uterine segment Caesarean section under general anaesthesia*

	MWT		PCEA		Infusion		*P*
Number	78		75		84		
Age (yr)	25.07 (16–37)		25.28 (16–34)		25.83 (17–40)		ns
Weight (kg)	68.66 (13.59)		71.51 (13.36)		70.63 (14.76)		ns
Height (m)	1.62 (0.01)		1.62 (0.05)		1.63 (0.01)		ns
Labour							
Spontaneous	22 (28.2%)		11 (14.7%)		14 (16.7%)		ns
Induced	26 (33.3%)		26 (34.7%)		33 (39.3%)		ns
Accelerated	30 (38.5%)		38 (50.7%)		37 (44%)		ns
Duration of 2nd stage (min)	96.98 (58.8) ($n = 59$)		94.15 (50.90) ($n = 60$)		98.73 (61.14) ($n = 62$)		ns
Delivery							
SVD	15 (19.2)		24 (32)		25 (29.8)		
LCFD	4	(57.7)	4	(46.7)	2	(46.4)	
MCFD	23		20		18		
KRFD	5		5		4		
Vent.	13		5		14		
MR/FD	0				1		
EmLUSCS,Ext.	12	(21.8)	13	(21.3)	15	(23.8)	
EmLUSCS,GA	5		3		5		
Assisted breech	1		0		0		

each study group to produce a total for each of the four pain scores, which was then expressed as a percentage of the total number of hourly assessments for each technique studied.

Maternal satisfaction was assessed as a retrospective measurement of the degree of pain relief experienced by the mother in the previous 1 h, thus taking into account any painful periods occurring during that time which would not necessarily be present at the time of assessment of the quality of analgesia. Satisfaction was scored as: 1 = satisfied; 2 = dissatisfied; 3 = very unhappy.

All women were interviewed within 24 h of delivery by an anaesthetist who was unaware of the technique used when pain relief was assessed again. The woman was asked to complete a linear analogue pain score representing her opinion of the overall efficacy of her analgesia, and to assess her analgesia as complete, good, acceptable or unacceptable for all, most or some of the time during the first stage and for delivery. The mode of delivery was also recorded.

Statistical analysis was carried out using Minitab (Version 7) running on an Amstrad 1640 PC. Analysis of variance, Kruskal–Wallis and chi square tests were applied where appropriate. $P < 0.05$ was considered significant. For clarity, a proportion of the results are expressed as a percentage, but statistical calculations were performed on actual numbers.

RESULTS

Patient characteristics are shown in table I. There were no significant differences between the three groups. Only primigravidae are included in the analyses ($n = 237$); there were insufficient numbers of multiparous patients.

Extradural data

Table II shows the extradural data from each of the three study groups. Mean duration of extradural block was similar in each group. Women in the infusion group received significantly greater doses of bupivacaine, the mean dose administered being 144.2 (SD 70.6) mg—approximately 30% greater than the mean dose administered in both the MWT and PCEA groups. The greater mean dose of bupivacaine resulted from a greater anaesthetist intervention rate required to continue effective extradural analgesia. The proportion of women requiring no or only one anaesthetic intervention was 89.3% in the PCEA group, 86.7% in the MWT group and 64.2% in the infusion group ($P < 0.05$). The total number of anaesthetic interventions was 49 in the PCEA group and 44 in the MWT group, compared with 120 in the infusion group ($P < 0.05$). Some mothers required several interventions.

Quality of analgesia

In the PCEA group, 21 women (28.4%) were pain free at all observations, compared with 26.2% in the infusion and 22.4% in the MWT groups (ns). Twenty women in the PCEA group (27%) recorded distressing pain at one or more of the hourly assessments (13 of whom experienced one or more complication of rectal pressure, unilateral block or missed segment). Similarly, in the infusion group 35 women (41.7%) recorded distressing pain at least once (21 with the above complications), and in the MWT group 26 women (34.2%) recorded distressing pain at least once (nine with the above complications) (ns).

There was no statistically significant difference in the cumulative scores of 3 (distressing pain or pressure) among the three groups (table III). However, of the total number of distressing pain

TABLE II. *Characteristics of extradural block: duration and dose (mean* (SD)), *and linear analogue pain scores (median)*

	MWT	PCEA	Infusion	P
Number	78	75	84	
Extradural duration (min)	369.1 (152.9)	383.5 (158.4)	384.5 (160.8)	ns
Mean bupivacaine dose (mg)	110.24 (57)	109.55 (58.1)	144.18 (70.6)	
Pain score (cm)				
Before extradural	7.2	7.5	7.5	ns
After extradural	0.65	1	0.65	ns

TABLE III. *Quality of analgesia, expressed as a percentage of all hourly observations for each score in all techniques. 0 = No pain or awareness of contractions; 1 = awareness of pressure or tightening; 2 = slight pain or pressure; 3 = distressing pain or pressure*

	MWT	PCEA	Infusion	P
Cumulative analgesia score (%)				
0	25.7	23.8	35	< 0.01
1	35.7	39.5	30.4	< 0.05
2	28.7	25.2	20.7	< 0.05
3	9.9	11.5	13.8	ns
Women scoring 3 at least once (%)	34.2	27	41.7	ns

TABLE IV. *Maternal satisfaction with analgesia provided, expressed as a percentage of all hourly observations for each score in all techniques. 1 = Satisfied; 2 = dissatisfied; 3 = very unhappy. No significant differences*

	MWT	PCEA	Infusion
Cumulative maternal satisfaction score (%)			
1	86	85	87.2
2	12	10	10.3
3	1.8	5	2.6
Women scoring 3 at least once (%)	7.8	13.3	13.2

episodes, significantly more were experienced by women in the MWT group in the absence of complications (MWT 6.1 %, PCEA 4.3 %, infusion 4.1 % ($P < 0.01$)).

The greatest proportion of cumulative scores of 2 (mild contraction or pressure pain) (28.7 %) occurred in the MWT group ($P < 0.05$).

The PCEA group experienced the greatest proportion of cumulative scores of 1 (painless tightening or pressure) (39.5 %) ($P < 0.05$).

The infusion group achieved the greatest proportion of cumulative scores of 0 (no sensation of contraction or pressure) (35 %) ($P < 0.01$).

Combining analgesia scores 0 and 1 provided the pain-free hourly recordings in each group: 61.4 % in MWT, 63.3 % in PCEA and 65.15 % in the infusion group (ns).

Maternal satisfaction

Fewer women in the MWT (7.8 %) were "very unhappy" (grade 3) with their pain relief at some time during their extradural analgesia, compared with 13.3 % in the PCEA and 13.2 % in the infusion groups (ns) (table IV). Similarly, there was no statistically significant difference between the cumulative satisfaction scores of 86.1 % in the MWT, 85 % in the PCEA and 87.2 % in the infusion groups (table IV).

Post-delivery questionnaire

In the MWT group, 44.9 % of women experienced complete pain relief throughout all or most of their extradural, compared with 52 % in the PCEA group, and 54.4 % in the infusion group (ns). Extradural analgesia failed completely in four of the 237 primigravida—two women in each of the MWT and PCEA groups. An additional 27 women experienced unacceptable pain: 11.5 % in the MWT group, 8 % in the PCEA and 14.8 % in the infusion group (ns).

Retrospective linear analogue pain score

There was no significant difference between median linear analogue pain scores of analgesia throughout the duration of the extradural block (table II).

Analgesia for delivery

Complete or good analgesia throughout delivery was experienced by 61.3 % in the PCEA group, 54.8 % in the infusion group and 38.5 % in the MWT group ($P < 0.025$). The proportion of women experiencing unacceptable pain for some of the time during their delivery was 2.8 % in the infusion group, 10 % in the MWT group and 16.9 % in the PCEA group ($P < 0.5$). No significant difference in the mode of delivery was noted in the three groups.

DISCUSSION

Controversy persists over the association between the degree of motor block and operative vaginal deliveries. For this reason, despite the superior analgesia produced by 0.5 % bupivacaine, 7–10 ml demand top-ups of 0.25 % bupivacaine administered by midwives has been the routine regimen for continuous extradural analgesia in this Unit [4]. In 1987, Purdy, Currie and Owen concluded that 0.375 % bupivacaine administered regularly in doses of 0.5 mg kg^{-1} was the optimum solution for a top-up technique, abolishing severe pain in all women [5]. To be effective, regular top-up techniques result inevitably in some women receiving interventions and bupivacaine when these are not required, resulting in a labour-intensive and potentially hazardous technique.

In 1985 Li, Rees and Rosen concluded that 0.125 % extradural bupivacaine delivered at an infusion rate of 10 ml h^{-1} offered the best compromise between significant prolongation of the block and patient safety [6]. In this study, 64.2% of women in the infusion group required no or only one anaesthetist-administered top-up, which is similar to the 69% recorded in Li's study and 76% in the study by Bogod, Rosen and Rees [7]. Both these studies established the extradural block with 0.5% bupivacaine 10 ml and in the case of Bogod's regimen, additional top-ups were also of 0.5% bupivacaine, which may explain their lower intervention rate. No infusion study using 0.125% has abolished severe pain in all women.

Recently, several authors have studied PCEA for analgesia in labour and shown this technique to provide a viable alternative for continuous extradural analgesia [1–3]. Using 0.125% bupivacaine with adrenaline 1 in 400000, Gambling and colleagues showed that, in most subjects, the PCEA regimen avoided the return of significant discomfort, but in six of 30 women studied additional analgesia was required [1]. PCEA dose requirements were reduced compared with a previous study of plain 0.125% bupivacaine with a background infusion [2]. Lysak, Eisenach and Dobson concluded that the optimum solution for PCEA was 0.125% bupivacaine with fentanyl 1 $\mu g\ ml^{-1}$ while the addition of adrenaline increased motor block [3]. Although sensory block extended above T6 in three of 46 women, no complications were noted.

For the past 9 years, the routine midwife top-up technique in this hospital has commenced with a 3-ml preliminary injection, and this volume was used for the PCEA top-ups with a lockout period of 5 min and a maximum hourly dose of 12 ml for safety. The exact timing and frequency of the PCEA top-up doses were controlled by the mother herself. Confidence in PCEA was gained quickly and no problems occurred with the Graseby PCEA pump. The solution was prepared simply without the hazards of dilution and anaesthetist top-ups could be given from the same syringe.

The need to deliver small 3-ml boluses and the resulting 15 min to deliver a 12-ml dose may prolong the painful episode. However, the high proportion of hourly satisfaction scores (85%) confirms its efficacy as a top-up technique. Request for anaesthetic intervention as soon as painful rectal pressure or unilateral block develop should result in earlier delivery of a larger volume or greater dose top-up, as occurred in our infusion group and may improve further PCEA.

As in the study by Lysak, Eisenach and Dobson [3], block extension above T7 occurred in seven mothers in the PCEA group without complication—five were receiving anaesthetist intervention. Transient mild hypotension occurred in one women, unrelated to top-ups, possibly because of venocaval occlusion.

The pain of labour is related to the force and frequency of uterine activity and is, initially at least, intermittent. As labour progresses, pain becomes more severe, longer lasting and more frequent. For this reason, it was believed that hourly assessment of pain might prove to be inadequate, as pain may occur between assessments and be relieved by top-ups. Hourly recordings of maternal satisfaction experienced during the preceding 1 h, although more subjective, would reflect the occurrence of any pain experienced. It might, therefore, be a more accurate measure of the pain occurring during what would, on hourly assessments alone, appear to be a satisfactory extradural block.

In this study, it would appear that direct hourly analgesic assessments are a more sensitive index of extradural efficacy than retrospective analysis, whether performed during labour or at post-partum interview later, despite the fears that painful periods may not coincide with the time of the assessment. Distressing pain, if of brief duration, does not appear to affect adversely the woman's assessment of the efficacy of extradural analgesia.

Despite the difference in delivery technique, surprisingly comparable analgesia was produced by the three regimens, achieving equivalent maternal satisfaction with no significant difference in the mode of delivery and no complications. While persistent distressing pain clearly reduces maternal satisfaction, experiencing slight pain was considered satisfactory analgesia by some women. Extradural infusions produced more intense analgesia and the PCEA technique was characterized by analgesia associated frequently with sensation of tightening or pressure. Some mothers were deliberately sparing with their top-ups, content to feel a degree of discomfort over which they knew they had control—an aspect they found particularly satisfying. In the MWT group, slight pain occurred more frequently.

It is clear from this study that, irrespective of the method of providing continuous extradural analgesia, a significant proportion of women experience episodes of distressing pain during an initially effective extradural block. Pain arises from several sources: regression of the block, a block of sufficient spread but insufficient intensity, or complications such as rectal pressure, unilateral block or missed segment. Failure to identify the cause of the pain allows it to persist. Some causes may be treated successfully by manipulation of the delivery technique, for example posture and block regression, while rectal pressure or unilateral block require immediate attention from the anaesthetist to ensure early elimination. The overall responsibility for ensuring effective analgesia is provided rests with the anaesthetist, but is dependent on continuous assessment of the woman's analgesia by the attending midwife.

This study has shown that PCEA was an effective and safe alternative for continuous extradural analgesia and was popular with mothers, midwives and anaesthetists. However, careful monitoring of the upper level of the block was required as, in seven mothers in the PCEA group, the block height was above T7.

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CARDIOVASCULAR SUPPORT DURING COMBINED EXTRADURAL AND GENERAL ANAESTHESIA

P. M. C. WRIGHT AND J. P. H. FEE

SUMMARY

We have examined the effect of prophylactic treatment with i.v. fluid 1000 ml, ephedrine 24 mg or methoxamine 4 mg on cardiovascular responses to both extradural and combined extradural and general isoflurane anaesthesia in 45 adult patients undergoing knee arthroplasty. Heart rate (HR) and systemic arterial pressure (AP) were measured using automated oscillotonometry and cardiac output was measured using continuous wave suprasternal Doppler ultrasonography. After lumbar extradural anaesthesia (LEA) there were no significant differences in arterial pressure between treatments, although cardiac index was significantly greater after fluid preloading (mean 4.3 (95% confidence interval 3.7–4.9) litre min^{-1} m^{-2}) than after ephedrine (3.1 (2.6–3.6) litre min^{-1} m^{-2}) or methoxamine (2.6 (2.0–3.2) litre min^{-1} m^{-2}). During combined LEA and general anaesthesia, systolic AP was significantly greater after ephedrine (114 (103–125) mm Hg) than after either preloading (98 (88–107) mm Hg) or methoxamine (97 (89–105) mm Hg). The reduction in AP after induction of general anaesthesia was associated with a decrease in cardiac index after fluid preloading and a decrease in vascular resistance after methoxamine.

KEY WORDS

Anaesthetic techniques: extradural-inhalation combination. Complications: hypotension. Sympathetic nervous system, pharmacology: ephedrine, methoxamine.

Suggested advantages of lumbar extradural anaesthesia (LEA) in the perioperative period include a reduced incidence of postoperative thromboembolism, reduced blood loss and improved postoperative analgesia [1]. In addition, recent work has suggested that surgical outcome may be improved after extradural anaesthesia and analgesia [2].

Extradural anaesthesia has been shown to reduce thromboembolism after knee arthroplasty [3, 4]. However, the presence of a thigh tourniquet obviates the other potential benefits of extradural anaesthesia: blood loss is already minimal and cannot be attenuated further, but hypertension associated with tourniquet inflation may be prevented [5]. In addition, adequate sensory block of the knee requires an extensive block, as the knee has a nerve supply from both lumbar and sacral nerve roots and good sacral block is difficult to achieve without large volumes of local anaesthetic. Combined LEA and general anaesthesia may be a potentially suitable technique for knee arthroplasty, but the combination results in a greater degree of hypotension than with each technique alone [6].

The purpose of this study was to compare the relative merits of i.v. fluid preloading, ephedrine and methoxamine as cardiovascular support during combined extradural and general anaesthesia in patients undergoing knee arthroplasty.

PATIENTS AND METHODS

This study was carried out with the approval of the University Medical Ethics Research Committee and informed written consent was given by each patient. We studied adult patients (age range 23–76 yr) in ASA categories I and II, undergoing knee arthroplasty. Patients were excluded if they had a haemoglobin concentration less than 10 g dl^{-1}, were receiving cardioactive medications, had a heart rhythm other than sinus or had evidence of aortic dilatation or unfolding on chest x-ray.

Patients were allocated randomly to one of three regimens intended to support the cardiovascular system during LEA and later combined LEA and general anaesthesia. One group received an i.v. fluid preload consisting of Dextran 70 in 0.9% sodium chloride 500 ml over 10 min preceding the main extradural injection and then 500 ml of Hartmann's solution during the 20 min after completion of the dose (group P). A second group received a bolus i.v. injection of ephedrine 12 mg 5 min after completion of the extradural injection and another 12 mg infused in 50 ml of 0.9% sodium chloride over the subsequent 15 min (group E). The remaining patients received a bolus i.v. injection of methoxamine 2 mg 5 min after completion of the extradural injection and a further 2 mg infused in 50 ml of 0.9% sodium chloride over the subsequent 15 min (group M). These doses of the vasopressors are known to be approximately equipotent at increasing the arterial pressure during regional anaesthesia [7].

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TABLE I. *Physical characteristics of the patients in the three groups (mean (range or* SD*)). BSA = Body surface area*

	Group P	Group E	Group M
Age (yr)	58 (23–75)	58 (24–76)	59 (26–75)
Weight (kg)	70 (12)	72 (12)	73 (10)
Height (m)	1.66 (0.09)	1.66 (0.09)	1.69 (0.13)
BSA (m^2)	1.77 (0.19)	1.79 (0.17)	1.81 (0.19)
Sex (M:F)	8:7	9:6	8:7

Anaesthetic technique

Premedication comprised temazepam 20 mg by mouth. On arrival of the patient in the anaesthetic room, a 14-gauge cannula was inserted in a forearm vein. An 18-gauge extradural cannula was placed through a 16-gauge Tuohy needle so that its tip was at the body of the third lumbar vertebra. The patient rested for 10 min and, after baseline variables were recorded, a test dose consisting of 2% lignocaine 3 ml was given through the extradural cannula. After 5 min, during which time the patients in group P received the i.v. fluid preload, a further 2% plain lignocaine 17 ml was injected over 2 min. Twenty minutes after completion of this injection, the extent of anaesthesia to pinprick was determined. General anaesthesia was induced with thiopentone sufficient to obtund the eyelash reflex and maintained subsequently with 66% nitrous oxide and isoflurane (controlled to an end-tidal concentration of 0.5% (Ohmeda 5330 agent monitor)) in oxygen, with the patient breathing spontaneously via a face mask and circle system. End-tidal carbon dioxide pressure was monitored and controlled within 10% of the initial value, although controlled ventilation was never required during this study.

Measurements

Heart rate (HR) and arterial pressure (AP) were measured using an automated oscillotonometer (Datascope Accutorr). Measurements were made immediately before the extradural injection, after the fluid preload and subsequently at 1-min intervals during extradural anaesthesia and at 2.5-min intervals after the induction of general anaesthesia. Cardiac output was measured non-invasively using continuous wave suprasternal Doppler ultrasonography with a dedicated commercially available signal analyser (Datascope Accucom); the physical characteristics required for the numerical representation of cardiac index were determined empirically. Measurements were made immediately before the extradural injection, after the i.v. fluid preload and at 2-min intervals during extradural anaesthesia and 5-min intervals during general anaesthesia and surgery. The patients were blinded to the treatment administered, but it was not possible to double-blind the treatment allocation as the i.v. fluid preload could not be concealed and the acute slowing in heart rate which follows a bolus of methoxamine is obvious to the investigator using the suprasternal Doppler probe. However, data were logged by computer unseen by the investigator, the computer program demanding two estimations of cardiac output at each time point, and not allowing further measurements.

Intraoperative ECG, AP, $P\mathrm{E}'_{CO_2}$ and Sp_{O_2} were monitored continuously, as was airway isoflurane concentration. Subjective symptoms after vasoconstrictor administration were recorded as they were volunteered. Adverse cardiovascular events (hypotension (systolic AP (SAP) < 100 mm Hg) or hypertension (SAP > 180 mm Hg), arrhythmias) were recorded during and for 4 h after the operation. During the subsequent hospital stay, clinically apparent surgical complications (wound infection, thromboembolic events and adverse cardiovascular events) were recorded.

Analysis of data

Parametric data are reported as mean (95% confidence intervals) and frequency data are represented as frequencies and percentage. The 95% confidence interval of the difference between the means is given where this is appropriate. Within-group changes were analysed using repeated measures analysis of variance and between-group comparisons made using one-way analysis of variance followed by Student–Newman–Keuls multiple range test. Statistical significance was assumed when $P < 0.05$.

RESULTS

We studied 45 patients—15 in each of the three groups. The groups were similar in age, weight, height and gender distribution (table I) and cardiovascular variables on admission (table II). The combination of the extradural block and general anaesthesia was adequate for surgery in all the patients.

Acute bolus drug effects

The administration of dextran 70 in saline 500 ml before extradural anaesthesia resulted in little change in HR or AP, but there was a significant increase in cardiac index (CI), from mean 3.03 (95% confidence interval 2.53–3.52) litre min^{-1} m^{-2} to 3.54 (2.96–3.57) litre min^{-1} m^{-2}. The mean maximum changes in measured variables after a bolus of either eph-

TABLE II. *Cardiovascular characteristics on admission to hospital and induction dose of sodium thiopentone (mean (*SD *or range))*

	Group P	Group E	Group M
HR (beat min^{-1})	74 (7)	71 (13)	69 (8)
Systolic AP (mm Hg)	139 (24)	132 (18)	135 (17)
Diastolic AP (mm Hg)	78 (9)	75 (7)	76 (10)
Thiopentone (mg kg^{-1})	4.3 (1.1)	4.2 (1.0)	4.2 (0.8)
Upper block height	T5 (T3–T8)	T5 (T2–T9)	T6 (T3–T9)
Lower block height	S3 (S2–S4)	S3 (S1–S4)	S3 (S1–S5)

TABLE III. *Mean (95% confidence intervals) maximum changes in cardiovascular variables in the 5 min after a bolus dose of vasopressor*

	Ephedrine ($n = 15$)	Methoxamine ($n = 15$)
HR (beat min^{-1})	9.5 (3.3–15.6)	−19 (−15 to −23)
Systolic AP (mm Hg)	21 (12–31)	23 (19–28)
Diastolic AP (mm Hg)	11.3 (6.8–15.8)	11.9 (7.8–16.1)
CI (litre min^{-1} m^{-2})	−0.15 (−0.42 to 0.12)	−0.83 (−0.44 to −1.20)

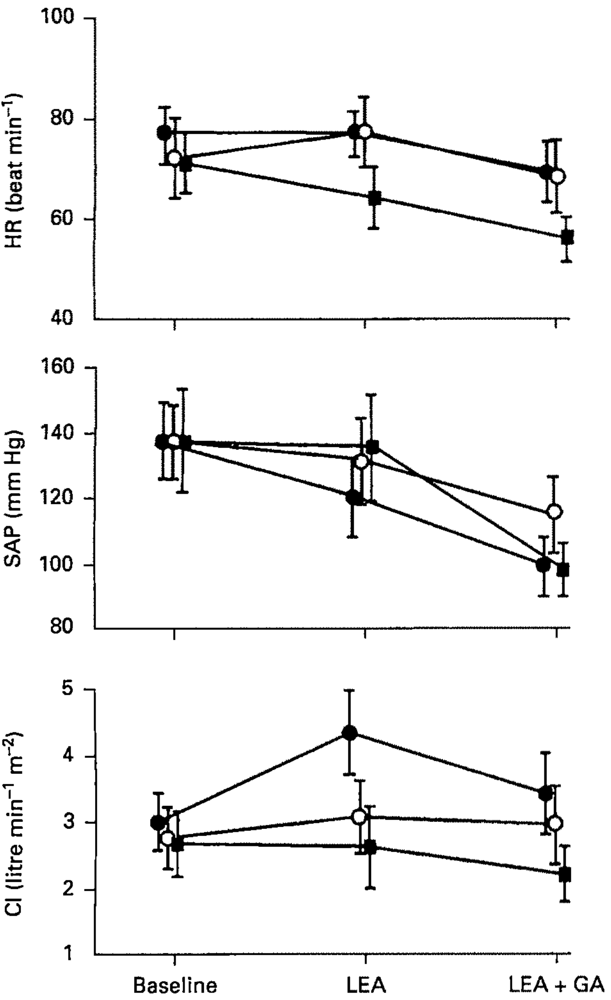

FIG. 1. Mean (95% confidence intervals) values of measured cardiovascular variables at baseline, during extradural anaesthesia and during combined extradural and general anaesthesia. ● = Preload; ○ = ephedrine; ■ = methoxamine.

edrine or methoxamine are shown in table III. The doses used were essentially equipotent in increasing both systolic and diastolic pressures, but while ephedrine increased HR, methoxamine resulted in a significant decrease, and while ephedrine had little effect on CI, methoxamine resulted in a significant reduction.

Changes during extradural anaesthesia

Values for HR, AP and CI were determined for each patient after the cardiovascular changes had reached a steady state at least 12 min after completion of the extradural injection. Systemic vascular resistance index (SVRI) and left ventricular minute work index (LVMWI) were determined using standard equations (central venous pressure was assumed to be constant). The changes in measured and derived variables associated with extradural anaesthesia in each of the three groups are shown in figures 1 and 2. HR decreased after methoxamine and was significantly reduced compared with either group P (95% confidence intervals for difference between means 5.1–20.2 beat min^{-1}) or group E (4.7–21.3 beat min^{-1}). Mean SAP in group P was significantly reduced compared with baseline and was markedly reduced compared with either group E (−5.6 to 26.6 mm Hg) or group M (−4.0 to 33.8 mm Hg). CI increased significantly in group P and was significantly greater than either group E (0.94–3.66 litre min^{-1} m^{-2}) or group M (1.59–4.55 litre min^{-1} m^{-2}). Mean SVRI remained unchanged in group M, but decreased significantly in group E and significantly more so in group P. LVMWI was significantly increased from baseline in group P and was significantly greater than the value in both vasoconstrictor groups.

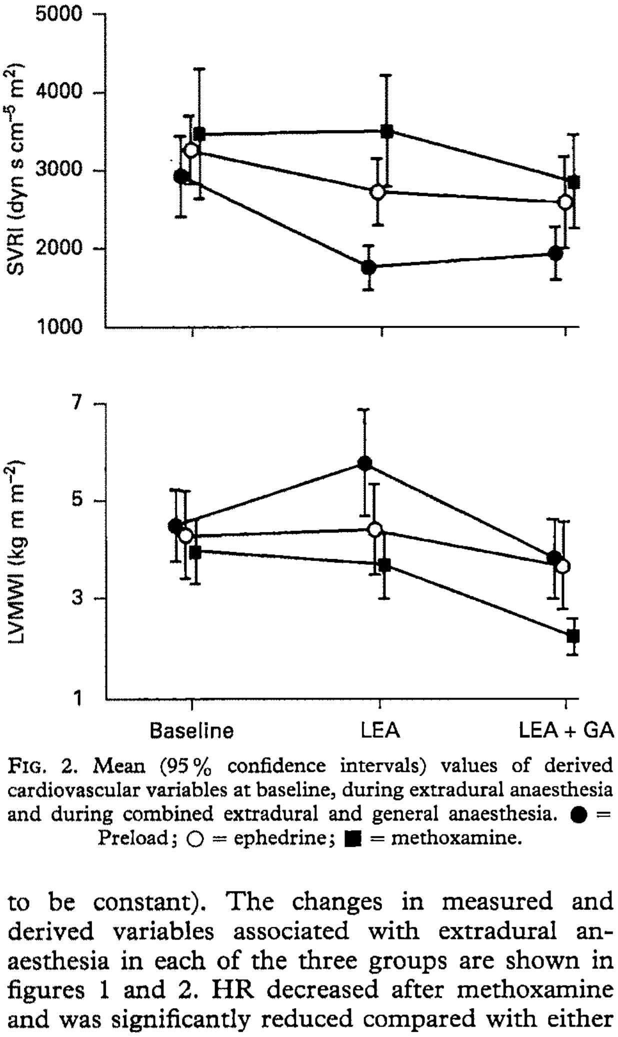

FIG. 2. Mean (95% confidence intervals) values of derived cardiovascular variables at baseline, during extradural anaesthesia and during combined extradural and general anaesthesia. ● = Preload; ○ = ephedrine; ■ = methoxamine.

Changes during combined extradural and general anaesthesia

Values of HR, AP and CI were determined and SVRI and LVMWI calculated for each patient at

TABLE IV. *Frequency of intraoperative and postoperative adverse events (number (frequency)). †Hypertension related to tourniquet inflation. ‡Patient developed fast atrial fibrillation 2 h after operation*

	Group P	Group E	Group M
Intraoperative event			
Hypertension (> 130% base)	1 (7)†	0 (0)	0 (0)
Hypotension (< 80 mm Hg)	7 (47)	2 (13)	5 (33)
Arrhythmias	0 (0)	0 (0)	0 (0)
Postoperative event			
Hypertension	0 (0)	1 (7)	1 (7)
Hypotension	2 (13)	2 (13)	4 (27)
Arrhythmias	0 (0)	1 (7)‡	0 (0)
Venous thrombosis	2 (13)	0 (0)	0 (0)
Pulmonary embolism	1 (7)	0 (0)	0 (0)

least 10 min after induction of general anaesthesia, but before tourniquet application or surgical stimulation; these values are also shown in figures 1 and 2. Heart rate reduced significantly in all groups after induction of general anaesthesia and that in group M continued to be reduced significantly compared with either group P (95% confidence interval for difference between means 6.7–20.3 beat min^{-1}) or group E (5.0–19.8 beat min^{-1}). SAP reduced significantly in all groups, but more so in groups P and M, and was significantly less in these two groups than in group E (2.0–29.0 mm Hg and 4.3–29.5 mm Hg compared with groups P and M, respectively). The induction of general anaesthesia resulted in a significant reduction in CI in group P, with relatively little alteration in the vasoconstrictor groups, although CI remained significantly greater in group P compared with group M (0.55–1.87 litre min^{-1} m^{-2}). Systemic vascular resistance reduced in groups M and E and after induction of general anaesthesia there were no significant differences between the groups.

Side effects

There were no subjective symptoms reported by the patients during extradural anaesthesia alone. Postoperative hypotension occurred in all groups and there was a single case of postoperative hypertension in each of the vasopressor groups (no significant differences between groups) (table IV).

DISCUSSION

We have found that, during extradural anaesthesia, both ephedrine and methoxamine, in appropriate dosage, were more effective at maintaining AP during extradural anaesthesia than fluid preloading; both achieved this by modulating decreases in SVRI that would normally occur as a result of extradural block. In addition, the combination of extradural anaesthesia and general anaesthesia, as expected, produced large reductions in AP [6, 8–10]. The reductions were greatest in the fluid preloading and methoxamine groups after large decreases in cardiac output and systemic vascular resistance, respectively.

The method used here to measure cardiac output (suprasternal continuous wave Doppler) is subject to errors and uncertainties; this subject has been discussed extensively elsewhere [11, 12]. Probably the major source of error with this technique is the determination of aortic cross-sectional area. In an investigation such as this, which is concerned with relative changes with time, such error as does arise from this source should remain the same in each patient and should be unimportant, especially as suprasternal Doppler actually measures the aortic minute distance which is proportional to CI [13] (hence the presentation of cardiac output as indexed to body surface area throughout this study). The accuracy of the device used in this study (Datascope Accucom) in tracking changes in a particular patient has been reported previously [14].

The circulatory effects of extradural anaesthesia have been investigated extensively. If the upper level of block is maintained below T2 in normal healthy supine volunteers, little decrease in AP is to be expected [15], although any degree of hypovolaemia may result in severe circulatory depression [16]. When hypotension does develop, it is a result of failure of venous return [17], as cardiac output must be maintained at much greater values than normal to compensate for reductions in systemic vascular resistance. The patients in this study who received the fluid preload did experience a reduction in AP, the most likely explanation for which is their greater age compared with subjects in previous studies [18].

The efficacy of i.v. fluid preloading to support AP during regional anaesthesia in an ageing population has been questioned [19] and this study was designed to evaluate vasoconstrictors as an alternative. Both ephedrine and methoxamine were effective in maintaining AP during LEA alone. Previous work carried out during treatment, rather than prophylaxis of hypotension, has indicated that bolus doses of methoxamine briefly decrease cardiac output [7] and bolus doses of ephedrine increase it in both obstetric [20] and non-obstetric [7] patients. During this study, the vasoconstrictors were given prophylactically and, although the brief reduction in cardiac output after methoxamine was confirmed, ephedrine had little effect on cardiac output.

The cardiovascular effects of combined extradural and general anaesthesia have received relatively little attention in the literature to date. A high incidence of hypotension was recorded during earlier studies [8, 10] and further reductions in AP when adrenaline was used with the extradural solution also have been documented [9]. The failure to sustain cardiac output after induction of isoflurane anaesthesia observed in the fluid preload group was similar to that observed with halothane anaesthesia [6]. The possibility that this resulted from interaction with circulating lignocaine has been discounted elsewhere [21]. Isoflurane has cardiac effects which differ from those of halothane and the reason why cardiac output should decrease with isoflurane during extradural anaesthesia remains obscure. Cardiac output is normally maintained during isoflurane administration as a result of sympathetic stimulation, and we can only speculate that, in the presence of extradural anaesthesia, increases in sympathetic outflow are unavailable to compensate for its direct cardiac effects [22].

The different responses in the two vasoconstrictor groups after the induction of general anaesthesia represent some of the most interesting findings of this study. After ephedrine, both cardiac output and systemic vascular resistance altered little after introduction of isoflurane, so that AP altered little. In contrast, after methoxamine, systemic vascular resistance decreased immediately after introduction of isoflurane. This failure of methoxamine to maintain SVR during general anaesthesia was unexpected, as the action of another alpha$_1$ adrenergic agonist drug, phenylephrine, is unaltered in the presence of halothane [23].

It has been argued that the use of vasoconstrictor drugs as prophylaxis against hypotension during regional block is illogical, as hypotension is a result of a failure of venous return [17]. However, by maintaining SVR at pre-block values they reduce the need for an increase in cardiac output and make the failure of venous return less likely in patients under extradural block. Methoxamine failed to maintain SVR after nitrous oxide–isoflurane, while preloading failed to maintain cardiac output after nitrous oxide–isoflurane; with both regimens there was a large reduction in AP with a combined anaesthetic technique. Prophylactic ephedrine has been recommended during spinal anaesthesia for patients in ASA category III because of its stabilizing effect on arterial pressure [24]. We have demonstrated that it maintains systemic vascular resistance during both extradural and combined extradural and general anaesthesia and we suggest that it offers advantages over either fluid loading or methoxamine for adult patients during these types of anaesthesia.

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SPINAL ANAESTHESIA FOR CAESAREAN SECTION: 0.125% PLAIN BUPIVACAINE 12 ML COMPARED WITH 0.5% PLAIN BUPIVACAINE 3 ML

M. VUCEVIC AND I. F. RUSSELL

SUMMARY

Forty women had elective Caesarean section under spinal anaesthesia with either 0.5% bupivacaine 3 ml or 0.125% bupivacaine 12 ml, injected at a rate of 1 ml/5 s. For 30 min after the spinal injection, each patient lay on her right side. Compared with the patients given 3 ml, in those given bupivacaine 12 ml there was a significantly greater spread of block ($P < 0.02$ *for analgesia;* $P < 0.002$ *for touch) and significantly less variation in levels of block (*$P < 0.02$ *for analgesia;* $P < 0.04$ *for touch). However, within 5 min of placing the women in a supine, tilted (right hip up) position, there were no clinically or statistically significant differences in the levels of block between the two groups.*

KEY WORDS

Anaesthetic techniques: spinal. Anaesthesia: obstetric. Anaesthetics, local: bupivacaine.

The relationship between the volume of local anaesthetic injected for spinal anaesthesia and the final level of block is not clear. There has been general acceptance that with plain (non-glucose-containing) solutions larger volumes, irrespective of concentration or baricity, enhance spread of analgesia [1, 2]. However, more recent studies of plain solutions in which the total dose was kept constant and only the volume and concentration changed, do not support this view [3–6]. Similar comparative studies have not been performed in pregnant patients, but it has been observed [7] that 0.125% plain bupivacaine 10 ml (with adrenaline 1:800000) produces spinal blocks similar to those achieved with 2.5 ml of the 0.5% bupivacaine solution [8]. Furthermore, in a study of spinal infusions in pregnancy [9], final levels of block were similar with volumes and concentrations ranging from 3 ml of 0.5% to 18 ml of 0.083% plain bupivacaine (bupivacaine 15 mg).

In the latter study [9], at the end of the 30-min infusions it was noted that there was wide variation in levels of block, unrelated to the volume infused. When the women were turned to a supine tilted position, lower blocks (T9 and below) extended some 9–10 dermatomes, whereas higher blocks (above T9) only extended by four or five dermatomes.

This differential effect on the spread of high and low blocks by a change in posture could obscure the true effect of different volumes of injection. Thus in order to assess the effects of volume of injection, uninfluenced by posturally induced extension of the levels of block, it was decided to perform a double-blind comparison of 0.5% plain bupivacaine 3 ml with 0.125% plain bupivacaine 12 ml and to keep the patients in a lateral position for 30 min after the spinal injection.

PATIENTS AND METHODS

We studied 40 healthy women having elective Caesarean section under spinal anaesthesia. The study was approved by the hospital Ethics Committee and informed consent was obtained from all patients. The patients were allocated randomly to receive one of two subarachnoid solutions: 0.5% plain bupivacaine 3 ml (Astra Pharmaceuticals, Kings Langley, England) or 0.125% plain bupivacaine 12 ml. The 0.125% solution was made by diluting 0.5% bupivacaine 3 ml with 0.9% sodium chloride 9 ml (B. Braun Ltd, Aylesbury, England). The resulting specific gravities of the two solutions were identical (0.999) [data provided by Astra Pharmaceuticals, 1990].

Randomization was achieved by computer-generated codes placed in sealed envelopes and opened after the patient arrived in the anaesthetic room. All spinal anaesthetics were performed by one investigator (I.F.R.) and all assessments of sensory levels were carried out by the other (M.V.), who was not admitted to the anaesthetic room until the spinal tray had been cleared away, when the first mentioned investigator left the anaesthetic room and was not present during the assessment period.

Each patient was premedicated with oral ranitidine 150 mg (at 22:00 the night before surgery and 08:00 on the morning of surgery). Sodium citrate 30 ml (0.3 mol litre^{-1}) was administered orally immediately before surgery. A 16-gauge i.v. cannula was inserted into a vein at the left wrist and Hartmann's solution 1000 ml administered. Additional Hartmann's solution was administered during performance of the block. Non-invasive monitoring of arterial pressure

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was performed throughout the procedure (Dinamap 1846SX with integral printer; Critikon Inc., Tampa, Florida). Intermittent fetal auscultation was performed until the start of surgery. When surgery commenced, the patients breathed oxygen 4 litre min^{-1} via a face mask until the baby was delivered.

A double needle technique was used. With the patient in the right lateral position the extradural space was located at L3–4 with an 18-gauge needle, using a midline approach and loss of resistance to air; the bevel of the extradural needle faced the patient's side. A 110-mm, 26-gauge spinal needle with a Quincke point was passed through the extradural needle such that the bevels were opposed. The spinal injections were made at a rate of 1 ml/5 s. The spinal needle was then removed and an extradural catheter inserted so that 3 cm remained in the extradural space. No injection was made through the catheter at this time. After insertion of the extradural catheter, the patients were allowed to straighten their legs a little to adopt a more comfortable position.

Timing commenced from the start of the spinal injection. The patient was kept on her right side for 30 min while the levels of analgesia and anaesthesia were assessed at 5-min intervals. Analgesia and anaesthesia were defined as follows: analgesia = reduced sensation to pinprick; anaesthesia = complete absence of sensation to pinprick.

After the 30-min assessment, the patients were turned supine and the operating table tilted to a right hip-up position. Further assessments of levels of block were made 2, 5, 10, 15, 20, 30 and 60 min later. Surgery proceeded when an adequate anaesthetic level was achieved.

If anaesthesia was insufficient for surgery, a supplementary dose of 2% lignocaine with adrenaline 1:200000 was administered via the extradural catheter and no further data relating to that patient were used for study purposes.

Ephedrine was used in association with rapid infusion of Hartmann's solution, to treat hypotension.

With the exception of data relating to the patients' physical characteristics, all other data were subjected to non-parametric statistical tests: Mann–Whitney test for inter-group comparisons; the Wilcoxon matched pairs signed rank test for within-group comparisons (for example right side *vs* left side); the Kolmogorov–Smirnov two-sample test for comparing the variability of data. $P < 0.05$ was regarded as statistically significant.

RESULTS

Twenty women received 0.5% bupivacaine plain 3 ml and 20 received 0.125% bupivacaine 12 ml. There were no differences between the groups in age, height, weight, body mass index (BMI) or gestation (table I).

During the first 30 min when the patient was in the lateral position, both analgesia and anaesthesia spread to a significantly greater degree in the 12-ml group ($P < 0.02$ for analgesia; $P < 0.002$ for anaesthesia) (figs 1, 2). After 30 min, repositioning to the supine tilted position resulted in a statistically significant increase in levels of block in both groups (figs 1, 2). After the patient was turned, the extension of block in the 3-ml group was greater than that in the 12-ml group ($P < 0.03$ for analgesia and anaesthesia). Within 5 min of turning, there were no clinical or statistical differences between the two groups in analgesic levels and, by 15 min, levels of anaesthesia were similar.

After 10 min with the patient in the lateral position, analgesic levels in the 3-ml group were spread over a wider range than those of the 12-ml group ($P < 0.02$). This was true also for anaesthesia after 15 min ($P < 0.04$). This difference in the variability of levels of block between patients in the groups was not present within 5 min of turning.

There was a greater need for extradural anaesthesia in the 3-ml group compared with the 12-ml group (chi-square, $P < 0.004$) (table II).

(Full details of levels of block are given for 0.5% bupivacaine 3 ml in Appendix A (tables III and IV) and for 0.125% bupivacaine 12 ml in Appendix B (tables V and VI).)

While the patients were in the lateral position, the arterial pressure was less in the 12-ml group ($P < 0.04$). Although eight women in the 12-ml group, compared with three in the 3-ml group, had a transient decrease in systolic arterial pressure greater than 30% during this period, this difference was not statistically significant (chi-square, $P < 0.07$).

More ephedrine was required in the 12-ml group, but this was not statistically significant ($P < 0.07$).

One patient in the 12-ml group had a dural tap with the catheter which was then left in the subarachnoid space. As the spinal anaesthesia behaved as expected, and no drug was injected down the catheter, her results have been included in the analysis. Neither this patient nor any other had a spinal headache.

DISCUSSION

These results indicate that when pregnant women at term remained on their sides after induction of spinal anaesthesia in the lateral position, the volume of injection played a significant role in the spread of spinal anaesthesia. However, when the patients were repositioned supine on a wedge, differential extension of block levels between high and low blocks resulted in all patients achieving similar final levels—an observation noted previously [9].

After the patients were turned, enhanced spread in the 3-ml compared with the 12-ml group is unlikely

TABLE I. *Patient characteristics (mean (range))*

	Bupivacaine group	
	0.5% 3 ml	0.125% 12 ml
n	20	20
Age (yr)	27 (24–30)	27 (23–32)
Height (cm)	161 (155–164)	163 (159–165)
Weight (kg)	74 (69–81)	76 (70–80)
BMI (kg m^{-2})	29 (27–33)	28 (27–31)
Gestation (weeks)	38 (37–39)	38 (38–39)

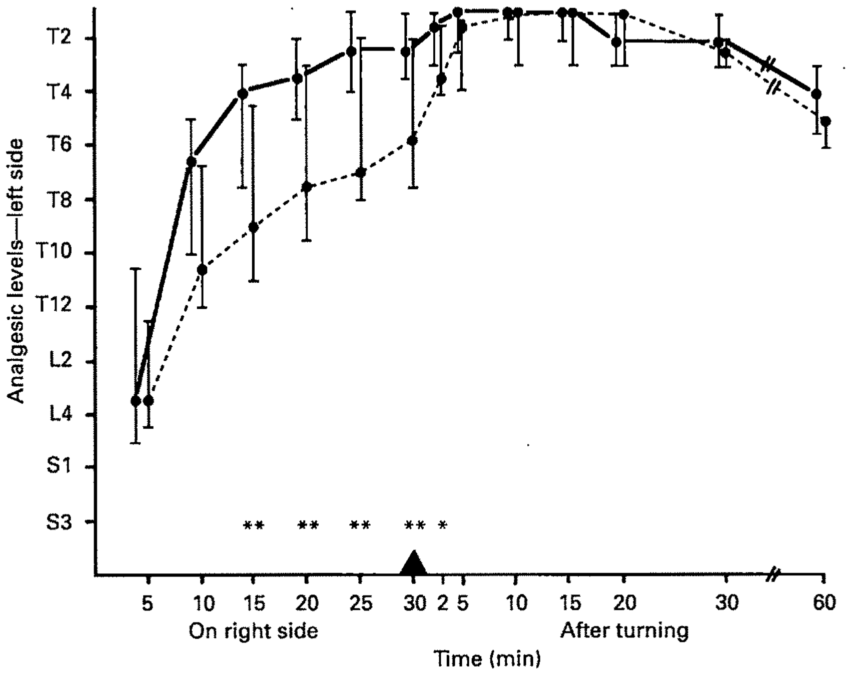

FIG. 1. Onset and spread of left side analgesic levels after spinal injection of either 0.125 % plain bupivacaine 12 ml (——) or 0.5 % plain bupivacaine 3 ml (---). The patients lay on their right side for 30 min (measured from the start of the injection) and were then turned supine with a right hip-up tilt (▲). Median values with upper and lower quartiles. $^*P < 0.05$, $^{**}P < 0.01$.

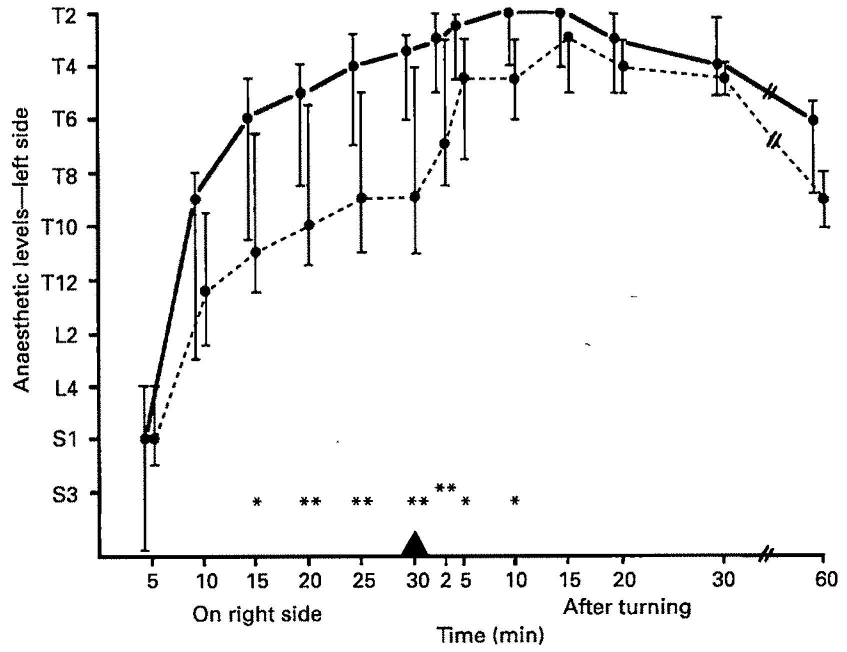

FIG. 2. Onset and spread of left side anaesthetic levels after spinal injection of either 0.125 % plain bupivacaine 12 ml (——) or 0.5 % plain bupivacaine 3 ml (---). The patients lay on their right side for 30 min (measured from the start of the injection) and were then turned supine with a right hip-up tilt (▲). Median values with upper and lower quartiles. $^*P < 0.05$, $^{**}P < 0.01$.

TABLE II. *Cumulative number of top-ups required at various time intervals after turning for the two study groups*

	Time after turning (min)						
Group	2	5	10	15	20	30	60
3 ml	—	4	5	5	5	6	9
12 ml	—	—	—	—	1	1	2

to be a result of the drug itself (the density of the two solutions is the same), but rather a result of limited spread of the drug in the lateral position and rostral displacement of CSF from the lower lumbar spinal canal secondary to venous engorgement [10–12]. The spinal canal is inelastic, and the overall CSF pressure is unaltered by change in posture from lateral to supine [13]. Thus any venous engorgement within the lumbar spinal canal must cause a reciprocal loss of fluid elsewhere within the spinal canal. A possible compensatory mechanism, which could explain the above results, would be movement of CSF from the lumbar region with subsequent displacement of venous blood from the spinal canal above the level of the vena caval occlusion. The further up the spinal canal were that movement, away from the lumbar area, the greater would be the available venous compensation between that point and the level of caval occlusion. Thus local anaesthetic drugs, already mixed with CSF, and extending to the T4 level (in the lateral position) would be affected minimally by translocation of CSF from the lumbar area (after repositioning) because compensatory mechanisms below T4 are able to "absorb" the displaced CSF. However, local anaesthetic mixed with CSF but extending only to the T10 level (in the lateral position) could be carried in a wave of CSF up the spinal canal as far as is required for venous compensation to occur. In this respect, it is of interest to note that mass movement of CSF is not a new idea. While Barker [14] emphasized the influence of gravity on the disposition of "heavy" spinal anaesthetics, he implied that drugs unaffected by gravity could reach the upper thoracic spinal canal "by shifting of the whole column of the cerebro-spinal fluid in which it is suspended upwards". However, such single compartment glass spines cannot simulate mass movement of CSF and are poor models for studying the spread of isobaric or near isobaric drug solutions.

As mass movements of CSF could also influence the distribution of truly isobaric solutions and this aspect has never been investigated in detail, it may be premature to suggest that posture has no effect on the spread of isobaric solutions [2, 15].

More patients in the 3-ml group required extradural anaesthesia and were excluded, suggesting that, compared with the 12-ml group, the density of block was less intense. With the patients in the lateral position, the bupivacaine in the 3-ml group would bathe the cord over a restricted area for 30 min, resulting in a dense block. Because of tissue fixation, less drug would then be available to be carried to the upper spinal canal on repositioning. In the 12-ml group there was a more even spread of local anaesthesia and block levels were already adequate for surgery before the patients were turned.

These results indicate that for 0.5% plain bupivacaine 3 ml to reach the upper thoracic dermatomes and be a reliable spinal anaesthetic for lower segment Caesarean section, it must depend on the movement of CSF to carry it to the upper thoracic spinal canal. This may help to explain why plain 0.5% bupivacaine has acquired a reputation as an unpredictable spinal anaesthetic.

APPENDIX A

LEFT-SIDED LEVELS OF ANALGESIA AFTER 0.5% BUPIVACAINE 3.0 ML

TABLE III. *Analgesia levels. Lateral position*: — = *no level assessable. Supine tilted position*: — = *extradural local anaesthetic required* (*no further assessment of block*)

Patient No.		Right lateral						Supine tilt						
	Time (min):	5	10	15	20	25	30	2	5	10	15	20	30	60
2		T12	T10	T10	T7	T7	T6	T5	T1	T1	T1	T1	T3	T5
5		—	T11	T9	T7	T3	T3	T1	T1	T1	T1	T1	T2	T6
6		L4	L2	L1	T12	T11	T11	T11	—	—	—	—	—	—
7		L5	T11	T10	T9	T7	T7	T7	—	—	—	—	—	—
9		L1	T12	T11	T8	T7	T7	T7	—	—	—	—	—	—
10		L4	T12	T12	T10	T7	T4	T4	—	—	—	—	—	—
11		L1	T9	T9	T9	T8	T8	T7	T7	—	—	—	—	—
13		T8	T3	T1	T1	T1	T1	T1	T1	T1	T1	T2	T3	T5
18		L5	T4	T4	T2	T2	T2	T2	T2	T2	T2	T2	T2	T5
20		L4	L2	T11	T11	T10	T10	T9	T6	T6	T6	T5	—	—
22		T10	T4	T3	T3	T2	T2	T1	T1	T1	T1	T1	T3	T5
24		L1	T9	T9	T7	T7	T7	T4	T1	T1	T1	T1	T1	T5
28		L4	T4	T2	T2	T2	T1	T1	T1	T1	T1	T1	T2	T4
29		T8	T6	T5	T3	T2	T2	T1	T3	T3	T3	T3	T3	T3
31		L5	L4	L4	T12	T12	T11	T9	T9	T9	T6	T4	T3	—
32		T11	T7	T4	T3	T2	T2	T1	T1	T1	T1	T1	T1	—
35		L4	T12	T11	T10	T9	T9	T4	T1	T1	T1	T1	T2	T5
37		L1	T9	T5	T5	T5	T4	T2	T2	T2	T2	T2	T4	T7
38		—	L4	L3	T8	T6	T6	T4	T3	T3	T1	T1	T2	T6
40		L3	T11	T9	T9	T8	T7	T5	T5	T4	T3	T3	T3	—

LEFT-SIDED LEVELS OF ANAESTHESIA AFTER 0.5% BUPIVACAINE 3.0 ML

TABLE IV. *Anaesthesia levels. Lateral position*: — = *no level assessable. Supine tilted position*: — = *extradural local anaesthetic required (no further assessment of block)*

Patient No.		Right lateral						Supine tilt						
	Time (min):	5	10	15	20	25	30	2	5	10	15	20	30	60
2		L3	T11	T11	T11	T11	T11	T8	T4	T4	T4	T4	T7	T8
5		—	L1	T10	T9	T5	T4	T3	T3	T3	T3	T3	T4	T9
6		—	L3	L2	L1	T12	T12	T12	—	—	—	—	—	—
7		—	L5	T11	T10	T8	T8	T8	—	—	—	—	—	—
9		S2	L1	T12	T10	T9	T9	T7	—	—	—	—	—	—
10		L5	L2	L1	T12	T10	T7	T7	—	—	—	—	—	—
11		—	T12	T12	T10	T9	T9	T8	T8	—	—	—	—	—
13		T9	T4	T3	T2	T2	T2	T2	T2	T2	T2	T3	T5	T9
18		S2	T9	T5	T5	T4	T3	T4	T4	T4	T3	T3	T4	T9
20		—	L3	L1	T12	T11	T11	T11	T10	T9	T9	T8	—	—
22		L4	T6	T6	T6	T5	T4	T3	T3	T3	T3	T4	T5	T8
24		—	T11	T11	T10	T10	T10	T9	T5	T5	T5	T5	T5	T9
28		L5	T10	T4	T4	T4	T3	T3	T3	T2	T2	T2	T4	T10
29		T10	T9	T7	T5	T5	T5	T3	T4	T5	T5	T5	T6	T6
31		S2	L5	L5	L2	L2	T12	T10	T10	T10	T8	T5	T4	—
32		L3	T9	T6	T5	T3	T3	T2	T2	T2	T2	T2	T4	—
35		L5	L1	T12	T11	T10	T10	T10	T9	T6	T3	T3	T4	T11
37		—	T11	T10	T9	T9	T9	T8	T7	T7	T6	T6	T7	T10
38		—	S1	S1	L3	T11	T11	T7	T6	T6	T3	T4	T4	T11
40		L4	L2	T11	T11	T11	T11	T6	T6	T5	T5	T5	T5	—

APPENDIX B

LEFT-SIDED LEVELS OF ANALGESIA AFTER 0.125% BUPIVACAINE 12.0 ML

TABLE V. *Analgesia levels. Lateral position*: — = *no level assessable. Supine tilted position*: — = *extradural local anaesthetic required (no further assessment of block)*

Patient No.		Right lateral						Supine tilt						
	Time (min):	5	10	15	20	25	30	2	5	10	15	20	30	60
1		T10	T10	T10	T7	T6	T6	T5	T5	T4	T4	—	—	—
3		T10	T8	T3	T1	T1	T1	T1	T1	T1	T1	T1	T2	T2
4		T12	T10	T7	T5	T4	T4	T3	T2	T1	T1	T2	T3	T3
8		L5	T5	T3	T2	T1	T1	T1	T1	T1	T1	T1	T1	T8
12		L4	T4	T4	T4	T1	T1	T1	T1	T1	T1	T2	T3	T9
14		S2	T12	T4	T4	T4	T4	T4	T2	T2	T2	T2	T4	T11
15		S1	L4	T12	T9	T7	T5	T5	T4	T2	T2	T2	T2	—
16		S2	T6	T4	T4	T4	T3	T3	T2	T2	T2	T3	T4	T10
17		L3	T6	T4	T2	T2	T2	T1	T1	T1	T2	T2	T2	T5
19		T7	T5	T2	T2	T2	T2	T2	T1	T1	T1	T1	T2	T6
21		T8	T6	T4	T2	T1	T1	T1	T1	T1	T1	T1	T1	T2
23		L5	T7	T5	T3	T1	T1	T1	T1	T1	T1	T1	T2	T4
25		T11	T6	T3	T3	T3	T3	T1	T1	T1	T1	T1	T1	T3
26		T11	T4	T3	T2	T2	T2	T1	T1	T1	T1	T1	T1	T5
27		L5	T1	T1	T1	T1	T1	T1	T1	T1	T1	T2	T2	T4
30		L4	T3	T2	T2	T2	T2	T1	T1	T1	T1	T1	T1	T2
33		S1	L4	T8	T5	T4	T3	T3	T3	T2	T2	T2	T3	T6
34		T11	T8	T8	T6	T4	T3	T3	T3	T3	T3	T3	T3	T4
36		L4	T7	T4	T4	T4	T4	T2	T2	T1	T1	T1	T1	T4
39		L4	L1	T10	T8	T5	T3	T3	T3	T1	T1	T1	T1	T4

LEFT-SIDED LEVELS OF ANAESTHESIA AFTER 0.125 % BUPIVACAINE 12.0 ML

TABLE VI. *Anaesthesia levels. Lateral position*: — = *no level assessable. Supine tilted position*: — = *extradural local anaesthetic required* (*no further assessment of block*)

Patient No.		Right lateral						Supine tilt						
	Time (min):	5	10	15	20	25	30	2	5	10	15	20	30	60
1		—	L1	L1	T12	T12	T10	T7	T7	T7	T7	—	—	—
3		S1	S1	T7	T4	T3	T3	T3	T3	T3	T3	T3	T4	T5
4		T12	T12	T9	T8	T7	T6	T5	T4	T3	T3	T5	T5	T5
8		—	T6	T4	T2	T2	T2	T2	T2	T2	T2	T2	T2	T9
12		L5	L3	T7	T5	T4	T3	T2	T2	T2	T2	T3	T4	T12
14		S4	L1	T11	T7	T7	T7	T5	T5	T5	T5	T5	T6	L1
15		—	—	L4	T12	T11	T10	T7	T5	T5	T5	T5	T5	—
16		—	T8	T6	T5	T5	T4	T4	T3	T4	T4	T5	T7	T12
17		—	T9	T6	T4	T3	T3	T2	T2	T2	T2	T4	T5	T9
19		L4	T8	T5	T4	T3	T3	T3	T2	T2	T2	T2	T3	T11
21		T10	T8	T6	T5	T2	T2	T2	T2	T2	T2	T2	T2	T3
23		S2	T10	T6	T5	T2	T2	T2	T2	T2	T2	T2	T4	T6
25		L1	T9	T4	T4	T4	T4	T2	T2	T2	T2	T2	T2	T5
26		T8	T5	T4	T3	T3	T3	T2	T2	T2	T2	T2	T3	T6
27		L3	T3	T2	T2	T2	T2	T2	T2	T2	T2	T3	T3	T5
30		S2	T5	T4	T4	T4	T3	T2	T2	T2	T2	T2	T2	T3
33		—	S1	T10	T9	T6	T5	T5	T5	T4	T4	T4	T5	T9
34		—	—	S2	T10	T8	T8	T6	T6	T6	T6	T6	T6	T6
36		S1	T9	T6	T6	T5	T5	T4	T4	T3	T2	T2	T2	T5
39		—	L4	T11	T10	T8	T5	T5	T4	T2	T2	T3	T3	T5

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PLASMA CONCENTRATIONS OF LIGNOCAINE AFTER OBTURATOR NERVE BLOCK COMBINED WITH SPINAL ANAESTHESIA IN PATIENTS UNDERGOING TRANSURETHRAL RESECTION PROCEDURES

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SUMMARY

Bilateral obturator nerve block has become a widely accepted technique to avoid adductor contraction during transurethral resection of prostate or bladder tumours. However, little is known about plasma lignocaine concentrations after the block. We conducted this study to assess a safe dose of lignocaine for injection in obturator nerve block. Bilateral obturator nerve block was performed with the aid of a peripheral nerve stimulator in 12 patients after spinal anaesthesia. In group I (n = 6), patients received 2% lignocaine 10 ml (200 mg) for the block; those in group II (n = 6) received 2% lignocaine 15 ml (300 mg). The block was satisfactory and no single adductor contraction was observed in either group during surgery. The peak plasma concentrations of lignocaine were 2.28 (SD 0.29) μg ml⁻¹ and 3.75 (0.79) μg ml⁻¹ in groups I and II, respectively. The greatest plasma concentration was 5.07 μg ml⁻¹ in a patient of group II. There were no symptoms suggesting systemic toxicity. We conclude that bilateral obturator nerve block may be performed safely and effectively with 2% lignocaine 10 ml with the aid of a peripheral nerve stimulator in patients undergoing transurethral resection procedures with spinal anaesthesia.

KEY WORDS

Anaesthetics, local: lignocaine. Anaesthetic techniques, regional: obturator nerve block.

Although spinal anaesthesia is a good indication for the transurethral resection (TUR) of prostate or bladder tumours, inadvertent stimulation of the obturator nerve is one of the most disturbing phenomena, with a danger of bladder perforation [1, 2]. To alleviate this potential danger, use of a bilateral obturator nerve block has been advocated [3–5]. However, the block may be associated with a potential risk of systemic toxicity of local anaesthetics, because a relatively large dose of the drug (10–15 ml of 1.5 or 2% lignocaine) is injected for unilateral obturator nerve block [4]. Furthermore, the pharmacokinetics of local anaesthetics may be altered substantially in patients undergoing TUR, because of increased age [6] and superimposed spinal anaesthesia. To our knowledge, no controlled studies are available on the plasma concentration–time curve after obturator nerve block. Therefore we designed this study to investigate the safest dose of lignocaine for bilateral obturator nerve block in patients undergoing TUR procedures with spinal anaesthesia.

PATIENTS AND METHODS

We studied 12 patients undergoing TUR of prostate or urinary bladder tumours. They gave informed verbal consent to participate in the study, which was approved by the local Institutional Ethics Committee. All patients were premedicated with atropine 0.5 mg and hydroxyzine 25 mg i.m. 1 h before anaesthesia. A 22-gauge cannula was inserted into the left radial artery under local infiltration with 0.25% bupivacaine 0.5 ml for arterial pressure monitoring and blood sampling. Spinal anaesthesia was performed at the L4–5 space after local infiltration with 0.25% bupivacaine. After a free flow of the spinal fluid through a 22-gauge spinal needle was confirmed, 3 ml of hyperbaric local anaesthetic solution, Neopercamine S (a mixture of cinchocaine 7.2 mg and amethocaine 3.6 mg) was injected into the subarachnoid space. When the anaesthetic level reached T12, usually after 3 min, obturator nerve block was begun.

Bilateral obturator nerve block

The patient was placed in the supine position, with the legs slightly abducted. Obturator nerve block was performed using a specially designed insulated needle [7] and a peripheral nerve stimulator (DigiStim III, Neuro Technology, Houston, U.S.A.). The needle was connected to the cathode lead of the nerve stimulator and the surface of the patient via an ECG electrode to the anode. After palpation of the pubic tubercle, a site 2 cm lateral and 2.5 cm inferior to it was marked [8]. The needle was advanced through the point in a slightly medial and cephalad direction until contraction of the adductor was visible with every discharge with the

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TABLE I. *Patient characteristics (mean (SD)). No significant differences in age, body weight, height and duration of the operation between the groups*

	Group I ($n = 6$)	Group II ($n = 6$)
Volume of 2% lignocaine (ml)	10	15
Age (yr)	73 (64–78)	72 (64–84)
Body weight (kg)	52 (6)	57 (15)
Height (cm)	159 (8)	161 (8)
Duration of operation (min)	132 (20)	136 (20)

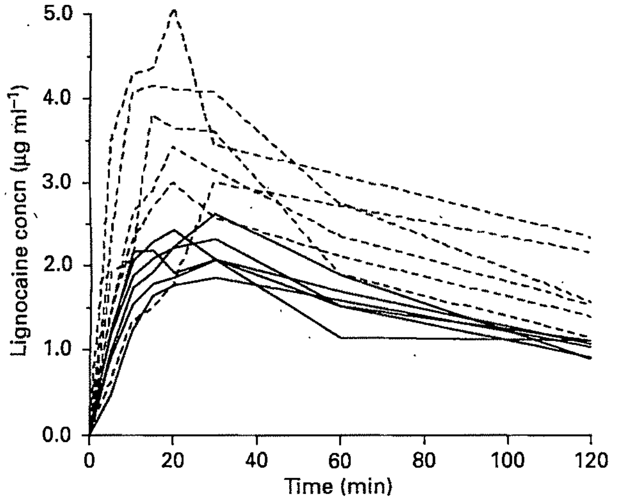

FIG. 1. Plasma lignocaine concentration–time curves after bilateral obturator nerve block with 2% lignocaine 10 ml (——) or 15 ml (---).

TABLE II. *Pharmacokinetic analysis of plasma lignocaine concentration after bilateral obturator nerve block with 2% lignocaine 10 ml (group I) or 15 ml (group II) (mean (SD)).* *$P < 0.05$ *compared with group I*

	Group I ($n = 6$)	Group II ($n = 6$)
Peak plasma concn (µg ml^{-1})	2.28 (0.29)	3.75 (0.79)*
Mass peak plasma concn for 100 mg injected (µg ml^{-1})	1.12 (0.14)	1.25 (0.26)
Time to peak plasma concn (min)	25.8 (6.7)	20.0 (5.5)
AUC$_{120}$ (µg ml^{-1} min)	182 (14)	292 (50)*

stimulator turned on. The block needle was advanced on the other side in the same way. Patients were allocated randomly to one of two groups. Bilateral obturator nerve block was performed in group I with 2% lignocaine 5 ml on each side and in group II with 2% lignocaine 7.5 ml on each side. The efficacy of the nerve block was confirmed by disappearance of adductor muscle contraction despite nerve stimulation, which occurred usually after injection of lignocaine 2–3 ml. Patients did not receive any sedatives or analgesics during operation.

Arterial blood samples (1-ml) were collected into glass tubes before obturator nerve block and at 5, 10, 15, 20, 30, 60 and 120 min after the injection of lignocaine. Plasma was separated by centrifugation and its lignocaine concentrations were determined by the fluorescence polarization immunoassay system (TDX system, Abbott Diagnostics, North Chicago) [9]. The detection limits of this method are 0.1–10.0 µg ml^{-1}, with acceptable precision (coefficient of variation = 3.0%). The cross-sensitivity of the assay to bupivacaine is less than 0.5%. The area under the plasma concentration–time curve for lignocaine (AUC$_{120}$) was calculated by the trapezoidal rule for 120 min.

Data are presented as mean (SD). Statistical analysis was performed by Student's t test for unpaired data. $P < 0.05$ was considered statistically significant.

RESULTS

There were no differences in age, weight, height or the duration of operation between the two groups (table I).

Obturator nerve block was carried out successfully in all patients of both groups. No contractions of the adductor muscle were observed during TUR procedures. There were also no symptoms suggesting CNS toxicity of local anaesthetics such as muscle twitch, dizziness or agitation, although drowsiness was noted in two patients in group II.

Peak plasma lignocaine concentrations were reached after 15–30 min for both groups (fig. 1). The greatest plasma concentrations were 2.62 µg ml^{-1} in a 69-yr-old patient in group I and 5.02 µg ml^{-1} in a 84-yr-old patient in group II. Although the mean peak plasma concentrations were significantly greater in group II than in group I, the mass mean peak plasma concentrations of lignocaine for every 100 mg injected were similar in both groups (table II). AUC$_{120}$ was also proportional to the dose injected (182 (14) µg ml^{-1} min and 292 (50) µg ml^{-1} min in groups I and II, respectively).

DISCUSSION

As the toxicity of local anaesthetics is related closely to their plasma concentrations, it is important for the safety of a neural block to define the plasma concentration–time curve. The present study using two different doses of lignocaine, 200 mg and 300 mg, for bilateral obturator nerve block indicated that plasma lignocaine concentration–time profiles were proportional to injected dose. The peak plasma lignocaine concentration after bilateral obturator nerve block, even with 2% lignocaine 15 ml, was less than 7 µg ml^{-1}, the concentration with the potential for systemic toxicity [10] and in the range 3.0–5.0 µg ml^{-1}, which is considered as a therapeutic concentration for antiarrhythmic effect [11]. Accordingly, bilateral obturator nerve block with the doses used in this study has a minimal risk for systemic toxicity in the elderly undergoing TUR with spinal anaesthesia. Clinically, there were also no symptoms suggesting systemic toxicity, although drowsiness was noted in two patients in group II. Nevertheless, no contraction of the adductor muscle was observed during TUR in either group. Therefore, we think 2% lignocaine 10 ml is sufficient for bilateral obturator nerve block.

We applied a peripheral nerve stimulator to the obturator nerve block to localize the nerve, because paraesthesiae cannot be elicited in a blind technique in patients with spinal anaesthesia. The efficacy of the block was verified also by disappearance of the adductor contraction through injection of lignocaine despite nerve stimulation. The block was performed easily with this technique, even though substantially smaller amounts of lignocaine were used compared with a previous report using a blind technique [4]. Magora and colleagues [8] also emphasized the advantage of using a peripheral nerve stimulator for obturator nerve block to obtain maximal effect with a minimal quantity of local anaesthetics, although they did not use spinal anaesthesia. Smith and Allison reported that sciatic nerve block may also be performed with a lower volume of local anaesthetics with the aid of a nerve stimulator [12].

Mayumi, Dohi and Takahashi [13] observed mean peak plasma concentrations of 3.26–4.11 $\mu g\ ml^{-1}$ 10 min after extradural anaesthesia with 2% lignocaine 10 ml, while a mean peak plasma concentration of lignocaine 3.75 (0.79) $\mu g\ ml^{-1}$ occurred after 15–30 min in group II of our study. The absorption rate of lignocaine after bilateral obturator nerve block under spinal anaesthesia is therefore similar to that after extradural block. The extent to which the decreased cardiac output with increased age and underlying spinal anaesthesia affected the absorption rate of lignocaine in our patients is unknown.

Spinal anaesthesia combined with bilateral obturator nerve block in elderly patients thus seems to be a relatively safe technique with a minimal risk of systemic toxicity. However, we believe that extradural anaesthesia should not be combined with bilateral obturator nerve block, as extradural anaesthesia also requires a significant volume of local anaesthetics. Based on the data of Mayumi, Dohi and Takahashi [13], the peak plasma concentration of lignocaine may reach toxic values if extradural anaesthesia is combined with obturator nerve block.

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INSPIRATORY TO END-TIDAL OXYGEN DIFFERENCE DURING NITROUS OXIDE ANAESTHESIA

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SUMMARY

In order to evaluate the value of the inspiratory to end-tidal oxygen concentration difference $(I_{O_2}-E'_{O_2})$ *as a monitor during general anaesthesia, we studied 40 orthopaedic patients allocated randomly to four groups: anaesthesia with enflurane or isoflurane in nitrous oxide with either spontaneous or controlled ventilation.* $(I_{O_2}-E'_{O_2})$ *followed an asymptotically increasing curve because of decreasing uptake of nitrous oxide. At 1 h,* $(I_{O_2}-E'_{O_2})$ *approached the end-tidal carbon dioxide concentration* (E'_{CO_2})*. During spontaneous ventilation,* $(I_{O_2}-E'_{O_2})$ *correlated best with* E'_{CO_2}*. During controlled ventilation, there was a negative correlation between* $(I_{O_2}-E'_{O_2})$ *and nitrous oxide uptake rate. Changes in oxygen uptake rate were reflected in* $(I_{O_2}-E'_{O_2})$*, provided that the total ventilation volume was constant and the nitrous oxide uptake rate approached steady state conditions.*

KEY WORDS

Anaesthesia: general. Anaesthetics, gases: nitrous oxide. Monitoring: inspiratory–end tidal oxygen difference.

Breath-by-breath analysis of oxygen concentration has become available recently through improvements in paramagnetic oxygen analysers [1, 2]. In addition to the inspiratory oxygen concentration (I_{O_2}), fast response oximetry gives end-tidal concentration (E'_{O_2}) and the inspiratory to end-tidal oxygen concentration difference $(I_{O_2}-E'_{O_2})$. In animal experiments, an increasing $(I_{O_2}-E'_{O_2})$ was the most sensitive indicator of hypoventilation and exceeded the sensitivity of end-tidal carbon dioxide (E'_{CO_2}) [3]. This finding has been confirmed during clinical anaesthesia [4]. $(I_{O_2}-E'_{O_2})$ theoretically reflects metabolism, circulation and ventilation. During nitrous oxide anaesthesia, uptake of nitrous oxide influences the end-tidal oxygen concentration as the expiratory volume decreases by the nitrous oxide uptake [5]. The interpretation of $(I_{O_2}-E'_{O_2})$ during anaesthesia is therefore complicated.

This study was undertaken to evaluate $(I_{O_2}-E'_{O_2})$ as a monitoring variable during nitrous oxide anaesthesia.

MATERIALS AND METHODS

The study was approved by the Ethics Committee of the University of Göteborg.

I_{O_2} and $(I_{O_2}-E'_{O_2})$ were measured between the Y-piece and the tracheal tube with a sampling paramagnetic analyser (Multicap, Datex Instrumentarium OY, Helsinki, Finland). The 10–90% response time was 150 ms, with a non-linearity error of less than ±1% [2]. E'_{CO_2} and inspiratory nitrous oxide concentration (I_{N_2O}) were measured by infra-red absorption in the Multicap.

A circle absorber system (Monosorb, Siemens-Elema, Solna, Sweden) of total volume 4.5 litre with a graded standing bellows was used. Expiratory total ventilation $(\dot{V}E)$ was measured between the tracheal tube and the Y-piece with a turbine vane transducer sensor of stated accuracy of ±8% (Ohmeda 5420, BOC Health Care Division).

Sampling gas from the gas analyser was returned to the circle system through a uni-directional valve placed before the absorption canister. The analyser was calibrated before and after each patient with a certified gas containing 3.0% carbon dioxide, 31% oxygen, 59% nitrous oxide and 7% nitrogen (AGA GAS AB, Stockholm, Sweden), and with 100% oxygen and 100% nitrous oxide. An anaesthetic agent monitor (Normac, Datex Instrumentarium OY, Helsinki, Finland) was calibrated according to the manufacturer's instructions, with a calibration gas. The displayed readings were within 0.05 vol% of the calibration gas. The oxygen and nitrous oxide flowmeters were calibrated with a Calibration Analyzer RT-200 (Timeter International Inc., Lancaster, PA 17601, U.S.A.). These flowmeters were checked also by the filling times of the Mylar bag used for the collection of excess gas.

Excess gas was collected every 10 min in a non-permeable Mylar bag connected to the spill valve. The gas pressure in the bag was measured during the collection period. When the pressure increased from −0.2 to 1.5 cm H_2O, the bag contained a gas volume of 660 ml. The time needed for this pressure increase was recorded every 10 min until completion of surgery. The excess gas flow could thereby be calculated. The gas contained in the Mylar bag was then analysed for oxygen and nitrous oxide concentrations.

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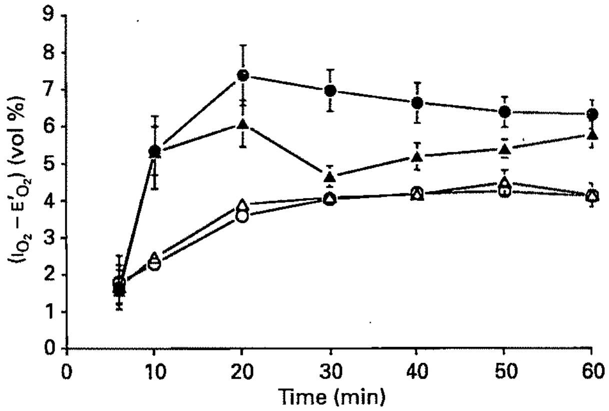

FIG. 1. Mean (SEM) inspiratory to end-tidal oxygen concentration difference $(\mathrm{I}_{\mathrm{O}_2} - \mathrm{E}'_{\mathrm{O}_2})$ during the first 1 h of anaesthesia. (● = Group ES; ▲ = group IS; ○ = group EC; △ = group IC).

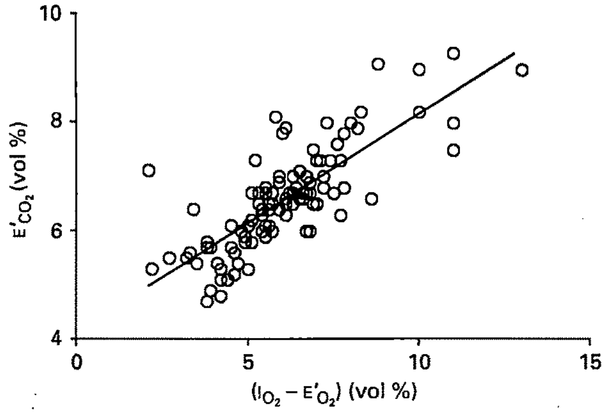

FIG. 2. Linear regression analysis of $(\mathrm{I}_{\mathrm{O}_2} - \mathrm{E}'_{\mathrm{O}_2})$ and $\mathrm{E}'_{\mathrm{CO}_2}$ during spontaneous ventilation (groups ES + IS). $y = 4.1 + 0.40x$ ($r = 0.79$; $P < 0.001$).

Calculations

Oxygen uptake ($\dot{V}\mathrm{O}_2$) was calculated from the oxygen flowmeter setting ($\dot{V}\mathrm{fg}_{\mathrm{O}_2}$), the excess gas flow ($\dot{V}\mathrm{ex}$) and the oxygen concentration in excess gas ($\mathrm{ex}_{\mathrm{O}_2}$):

$$\dot{V}\mathrm{O}_2 = \dot{V}\mathrm{fg}_{\mathrm{O}_2} - \dot{V}\mathrm{ex} \times \mathrm{ex}_{\mathrm{O}_2}$$

Similarly, nitrous oxide uptake ($\dot{V}\mathrm{N}_2\mathrm{O}$) was calculated from the nitrous oxide fresh gas flow ($\dot{V}\mathrm{fg}_{\mathrm{N}_2\mathrm{O}}$), the excess gas flow and the nitrous oxide concentration in the excess gas ($\mathrm{ex}_{\mathrm{N}_2\mathrm{O}}$):

$$\dot{V}\mathrm{N}_2\mathrm{O} = \dot{V}\mathrm{fg}_{\mathrm{N}_2\mathrm{O}} - \dot{V}\mathrm{ex} \times \mathrm{ex}_{\mathrm{N}_2\mathrm{O}}$$

Anaesthesia

The patients were premedicated with midazolam 1 mg i.v. Oxygen 10 litre min^{-1} was given by face mask for about 1 min. Anaesthesia was induced with thiopentone 4–5 mg kg^{-1}. The patients were given suxamethonium 1 mg kg^{-1} to facilitate tracheal intubation. After tracheal intubation, the flows of fresh gas to the circle system were oxygen 1.5 litre min^{-1} and nitrous oxide 3.5 litre min^{-1} for 6 min. The inhalation agent used was delivered by conventional vaporizers outside the circuit to the end-tidal concentration desired. During these first 6 min, ventilation was controlled so that $\mathrm{E}'_{\mathrm{CO}_2}$ 4.5 vol % was obtained.

Six minutes after tracheal intubation, low flow anaesthesia was started. $\dot{V}\mathrm{fg}_{\mathrm{O}_2}$ was set according to body weight. Patients with a body weight of less than 70 kg received oxygen 250 ml min^{-1}, those weighing 70–100 kg received 350 ml min^{-1}, and for patients with a body weight of more than 100 kg, 500 ml min^{-1} was used. $\dot{V}\mathrm{fg}_{\mathrm{N}_2\mathrm{O}}$ was adjusted to maintain $\mathrm{I}_{\mathrm{O}_2}$ 30 vol %. If the bellows were emptying, $\dot{V}\mathrm{fg}_{\mathrm{O}_2}$ was increased by 50 ml min^{-1}. Either enflurane or isoflurane was given with an end-tidal concentration maintained at 1.2 or 0.85 vol %, respectively. If it became necessary to increase the depth of anaesthesia during the course of anaesthesia, thiopentone 50 mg was given i.v.

After obtaining informed consent, we studied 40 ASA group I and II patients undergoing knee arthroscopy who were allocated randomly to one of four groups:

Group ES. Enflurane: end-tidal concentration maintained at 1.2 vol %. The patients breathed spontaneously after the initial 6 min described above.

Group EC. Enflurane as in group ES, but ventilation controlled to maintain an end-tidal carbon dioxide concentration of 4.5 vol %.

Group IS. Isoflurane: end-tidal concentration maintained at 0.85 vol %. Spontaneous breathing after 6 min.

Group IC. Isoflurane as in group IS, but ventilation controlled to maintain an end-tidal carbon dioxide concentration of 4.5 vol %.

Statistics

Statistical significance was tested with ANOVA and Fisher's PLSD test between groups during the first 1 h of anaesthesia, and with repeated measures ANOVA and Fisher's PLSD test within each group in association with the start of surgery. Linear regression analysis was used when appropriate. Statistical significance was assumed for values of $P < 0.05$.

RESULTS

The mean age of the 40 patients was 36 yr and mean weight 78 kg; 11 were women.

After the initial 6 min of controlled ventilation, the mean $(\mathrm{I}_{\mathrm{O}_2} - \mathrm{E}'_{\mathrm{O}_2})$ was 1.6–1.8 vol % in all groups (fig. 1). In the groups with continuous controlled ventilation, $(\mathrm{I}_{\mathrm{O}_2} - \mathrm{E}'_{\mathrm{O}_2})$ increased gradually to 4.3 vol % at 60 min. In the groups with spontaneous ventilation (groups ES and IS) $(\mathrm{I}_{\mathrm{O}_2} - \mathrm{E}'_{\mathrm{O}_2})$ increased rapidly to about 5.4 vol % at 10 min. At 60 min, the mean values were 6.5 and 5.9 vol % in groups ES and IS, respectively. At the first measurement with spontaneous ventilation (10 min after induction of anaesthesia) there were significant ($P < 0.05$) differences in $(\mathrm{I}_{\mathrm{O}_2} - \mathrm{E}'_{\mathrm{O}_2})$ between the groups with spontaneous ventilation and those with controlled ventilation. These differences persisted throughout the first 1 h, with the exception of the measurements at 30 and 40 min. At these measurements, $(\mathrm{I}_{\mathrm{O}_2} - \mathrm{E}'_{\mathrm{CO}_2})$ in group IS was not significantly different from the

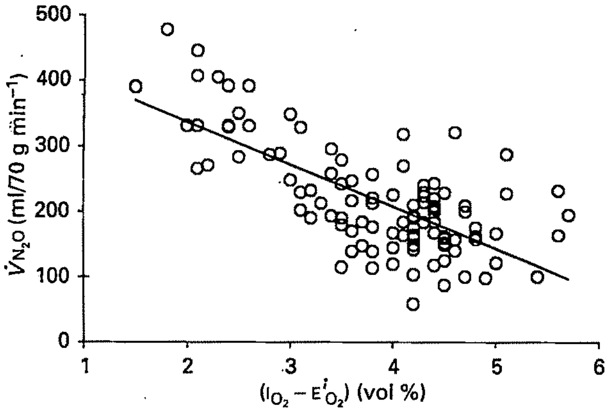

FIG. 3. Linear regression analysis of $(I_{O_2}-E'_{O_2})$ and $\dot{V}N_2O$ during controlled ventilation (groups EC+IC). $y = 468-65x$ ($r = 0.70$; $P < 0.001$).

values in groups IC or EC. Group ES had greater values of $(I_{O_2}-E'_{O_2})$ than group IS at 30, 40 and 50 min ($P < 0.05$ in all cases).

Linear regression analysis was used between $(I_{O_2}-E'_{O_2})$ and $\dot{V}O_2$, E'_{CO_2}, $\dot{V}E$ and $\dot{V}N_2O$. The strongest positive association was found between $(I_{O_2}-E'_{O_2})$ and E'_{CO_2} in the two groups with spontaneous ventilation (fig. 2). The relationship was:

$$E'_{CO_2} = 4.1 + 0.40 \times (I_{O_2}-E'_{O_2})$$

($r = 0.79, P < 0.001$).

A negative association was found between $(I_{O_2}-E'_{O_2})$ and nitrous oxide uptake during controlled ventilation (fig. 3). Linear regression analysis gave the formula:

$$\dot{V}N_2O = 468 - 65 \times (I_{O_2}-E'_{O_2})$$

($r = -0.70, P < 0.001$).

With the start of surgery (mean time 22–25 min after induction of anaesthesia in all groups), $(I_{O_2}-E'_{O_2})$ decreased in the groups with spontaneous ventilation ($P < 0.05$), whereas $(I_{O_2}-E'_{O_2})$ increased during controlled ventilation ($P < 0.05$) (table I). Associated mean values for ventilatory frequency, tidal volume, E'_{CO_2}, $\dot{V}O_2$ AND $\dot{V}N_2O$ are given also in table I. During controlled ventilation, a change in $\dot{V}O_2$ correlated significantly with a change in $(I_{O_2}-E'_{O_2})$ according to the formula:

$$\Delta\dot{V}O_2\ (\mathrm{ml\ kg^{-1}\ min^{-1}}) = -0.01 + 0.20 \times \Delta\,(I_{O_2}-E'_{O_2})$$

($r = 0.55, P < 0.05$).

DISCUSSION

Theoretically, one would expect $(I_{O_2}-E'_{O_2})$ to correlate positively with E'_{CO_2} and $\dot{V}O_2$ and negatively with $\dot{V}E$ and $\dot{V}N_2O$.

Assuming that the oxygram is an inversion of the capnogram and that the respiratory quotient is 1.0, $(I_{O_2}-E'_{O_2})$ should equal E'_{CO_2} during air breathing in steady state conditions. A respiratory quotient of less than 1.0 would result in an $(I_{O_2}-E'_{O_2})$ greater than E'_{CO_2}. This is usually not the case during the first 1 h of anaesthesia with 70 % nitrous oxide. At the start of a nitrous oxide anaesthetic, the uptake of nitrous oxide results in a difference between inspired and expired ventilatory volumes. The E'_{O_2} can therefore be greater than the I_{O_2}, despite a normal uptake of oxygen from the lungs—that is $(I_{O_2}-E'_{O_2})$ has a negative value [5]. Subsequently, as $\dot{V}N_2O$ decreases, $(I_{O_2}-E'_{O_2})$ increases. As the sum of the partial pressures of oxygen, carbon dioxide, nitrogen and anaesthetic gases must be constant, E'_{O_2} is dependent on E'_{CO_2} and on the end-tidal concentrations of anaesthetic gases. Thus E'_{O_2} decreases and $(I_{O_2}-E'_{O_2})$ increases with increasing E'_{CO_2} and E'_{N_2O}.

A possible advantage of $(I_{O_2}-E'_{O_2})$ in monitoring compared with E'_{CO_2} is its greater sensitivity to increases or decreases in respiratory gas exchange. This is probably a result of the small buffering capacity in the body for oxygen. Therefore, acute hypoventilation is detected by the $(I_{O_2}-E'_{O_2})$ before E'_{CO_2} [3, 4].

In this study, the displayed $(I_{O_2}-E'_{O_2})$ correlated best with E'_{CO_2} during spontaneous ventilation and with $\dot{V}N_2O$ during controlled ventilation. An approximation of the expected $(I_{O_2}-E'_{O_2})$ time course during nitrous oxide anaesthesia based on our results is:

$$(I_{O_2}-E'_{O_2})\ (\mathrm{vol\,\%}) = E'_{CO_2}\ (\mathrm{vol\,\%})/0.85 - 10 \times I_{N_2O}\ t^{-0.5}$$

where t represents time in minutes from the start of nitrous oxide anaesthesia.

The complexity of $(I_{O_2}-E'_{O_2})$ as a monitor was illustrated at the start of surgery. With spontaneous ventilation, the increased tidal volume and decreased E'_{CO_2} resulted in a decreased $(I_{O_2}-E'_{O_2})$. In contrast, during controlled ventilation an increased oxygen uptake and a decreased nitrous oxide uptake resulted in an increased inspiratory to end-tidal oxygen concentration difference.

TABLE I. *Respiratory variables before and after the start of surgery (mean (SD)). BS = Last measurement before the start of surgery; AS = first measurement after the start of surgery.* f = *ventilatory frequency*; V_T = *tidal volume*

	Ventilation			
	Spontaneous (Groups ES+IS)		Controlled (Groups EC+IC)	
	BS	AS	BS	AS
f (b.p.m.)	21.8 (4.9)	23.8 (5.5)	14	14
V_T (ml)	172 (45)	257 (59)	408 (97)	424 (108)
E'_{CO_2} (vol %)	6.9 (0.9)	6.4 (1.1)	4.5	4.5
$\dot{V}O_2$ (ml min^{-1})	186 (51)	222 (46)	183 (40)	194 (43)
$\dot{V}N_2O$ (ml min^{-1})	283 (105)	182 (49)	256 (74)	192 (65)
$(I_{O_2}-E'_{O_2})$ (vol %)	7.0 (2.2)	5.8 (1.6)	3.4 (0.9)	4.2 (0.7)

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A MODEL LUNG WITH DIRECT REPRESENTATION OF RESPIRATORY MUSCLE ACTIVITY†

J. S. MECKLENBURGH, T. A. A. AL-OBAIDI AND W. W. MAPLESON

SUMMARY

We describe the theory, construction and testing of an active model lung. This is designed so that when it is connected to a ventilator, the interaction between spontaneous ventilatory activity in the patient and the pressures and flows generated by the ventilator are reproduced faithfully. A waveform of negative pressure, pmus, *equivalent to the action of the respiratory muscles, is applied indirectly to the compliance unit of a conventional model lung. It is shown that, when the compliance and resistance of a subject have been measured, the waveform of* pmus *can be determined. This was undertaken in three volunteers breathing under various conditions, including connection to a ventilator operating in different modes. When these conditions were reproduced with the lung model replacing, but matched to, each subject, the original waveforms of flow and pressure at the mouth were reproduced.*

KEY WORDS

Lung: model. Measurement techniques: compliance, resistance. Ventilation: spontaneous.

A suitable model lung is required to test the performance of lung ventilators. A simple passive model is adequate to test ventilators which provide only controlled ventilation. Such a passive model lung usually comprises a compliance unit in series with a resistance unit [1, 2] to simulate the patient's total respiratory compliance and total respiratory resistance.

For ventilators which allow the patient to breathe spontaneously through them, an "active" model lung is required that simulates the patient's breathing. A flow-generating pump (for example a piston pump connected directly to the patient connection port of the breathing system) is adequate to determine the load imposed on the patient by the ventilator breathing system, provided the ventilator does not respond to the simulated patient activity [4]. However, these two models, passive lung and flow-generating pump, cannot be combined to reproduce the circumstances of spontaneous ventilatory activity combined with ventilator activity—as in intermittent mandatory ventilation (IMV) and pressure assistance.

Models have been described which allow both spontaneous breathing and machine induced-breaths to be reproduced, but the simulation is satisfactory only when the machine and spontaneous breaths occur at different times; when they coincide, the interaction may not be reproduced faithfully [4–7].

Therefore we have developed a model in which the activity of the respiratory muscles is represented by a pressure generator (and we have justified such a representation). Thus the pressure generator of the patient and the flow or pressure generator of the ventilator act together and separately on the impedances that lie between them. These impedances are the compliance and resistance of the respiratory system of the patient and those of the breathing system of the ventilator.

The objective of this study was first to design and construct a model lung which could reproduce not only the compliance and resistance, but also the pressure-generating properties of a given subject when connected to a given load or to a given ventilator with given settings. The second objective was to show that, when the model was set to simulate that subject under that condition and connected to that load or ventilator, the same waveforms of both flow and mouth pressure resulted. Three volunteer subjects were studied under widely varied conditions to provide a demanding test of the performance of the model.

THEORY, DESIGN AND CONSTRUCTION OF THE MODEL

Theory

Figure 1A shows a conceptual model of a patient breathing from a ventilator. The respiratory muscles apply a waveform of force to a "load" comprising the impedance of the respiratory system (total respiratory compliance, *C*, and total respiratory resistance, *R*) and the internal impedance of the ventilator. The ventilator also applies a force, in the form of a flow generator or pressure generator, to the opposite end of the impedances. The waveforms of flow, mouth pressure and volume which result are a consequence of the combined effects of the two forces on the combined impedances between them.

In the conceptual model, the waveform of force

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† A preliminary account of this work was presented to the Anaesthetic Research Society Meeting in Manchester, July 1985 [1].

produced by the respiratory muscles could be simulated exactly by paralysing those muscles and applying a waveform of negative pressure outside the thorax (fig. 1B), such that the waveforms of flow, volume and pressure at the mouth were as before. We term this waveform of negative pressure *p*mus. The symbol *P*mus (upper case) has been used by several previous workers [8–10] to describe the action of the respiratory muscles, but sometimes the mathematical definition is different and sometimes it refers only to the peak value under specified conditions. We use *p*mus (lower case) to refer to the instantaneous value of respiratory muscle activity throughout the ventilatory cycle—that is, the whole waveform. (This convention—upper case symbols for parameters and lower case for instantaneous values of variables—is adopted throughout this paper.)

It is shown in the Appendix that if the waveforms of mouth pressure, flow and volume are recorded from a subject, and the compliance and resistance are known from prior measurement, the waveform of *p*mus may be calculated from

$$p\text{mus} = p\text{m} - R.\dot{v} - \frac{v}{C} - P\text{AE}' \qquad (1)$$

where $p\text{m}$ = pressure at the "mouth"; R = total respiratory resistance; $\dot{v}$ = flow (inspiratory direction positive); v = volume of gas at ambient temperature and pressure (ATP) in the compliance unit in excess of that present at the end of the expiratory phase; C = total respiratory compliance; $P\text{AE}'$ = end-expiratory "alveolar" pressure.

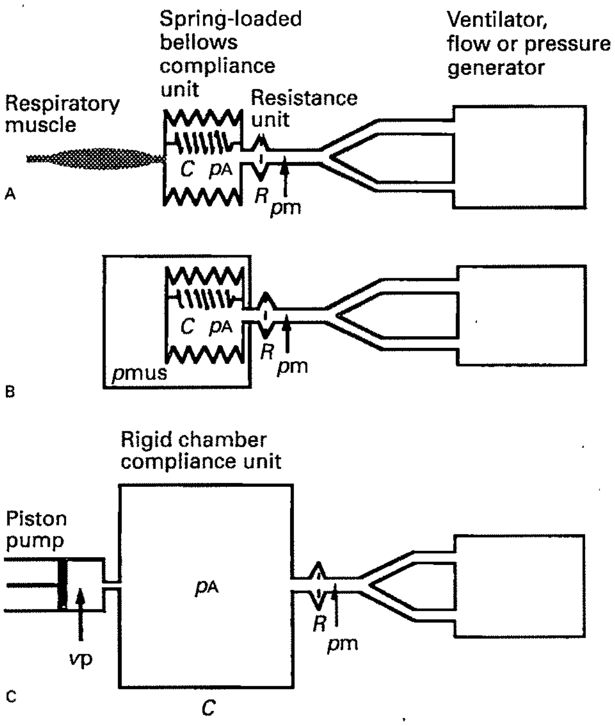
Spring-loaded bellows compliance unit
Ventilator, flow or pressure generator
Respiratory muscle
Resistance unit
C
pA
R
pm
A
C
pA
R
pm
pmus
B
Rigid chamber compliance unit
Piston pump
pA
R
pm
vp
C
C

FIG. 1. Models of a patient breathing from a ventilator. A: Conceptual model—respiratory muscles apply a waveform of force to the respiratory system. B: Directly equivalent mechanical model—a waveform of negative pressure (*p*mus) applies the same waveform of force. C: Adopted, indirectly equivalent, mechanical model (see text). C = Compliance of the compliance unit, equal to the total respiratory compliance of the subject; R = resistance of the resistance unit, equal to the total respiratory resistance of the subject; $p\text{A}$ = alveolar pressure; $p\text{m}$ = pressure at the mouth; *p*mus = waveform of force produced by respiratory muscles; $v\text{p}$ = change in volume of gas (at ATP) in the pump.

The amplitude and perhaps the waveform of *p*mus may be expected to vary between subjects and between conditions. However, if a mechanical model is constructed as in figure 1B, with the same compliance and resistance as the subject, and the same *p*mus waveform, as measured in the subject when connected to the ventilator with some settings of the controls, then if the model is connected to the ventilator with the same settings of its controls, the waveforms of flow, volume and mouth pressure would, ideally, be the same. Some discrepancies can be expected to arise from the fact that the impedance of the respiratory system is more complex than a single compliance in series with a single resistance [11]. However, the use of such two-component models is standard practice in ventilator testing [3, 12].

Theory of compliance and resistance measurement

The method used is based on multiple linear regression analysis as used by several authors [13–16]. Equation (1) can be re-arranged as:

$$p\text{m} = R.\dot{v} + \frac{1}{C}v + p\text{mus} + P\text{AE}' \qquad (2)$$

If the subject relaxes as fully as possible whilst connected to a ventilator set to provide continuous mandatory ventilation, *p*mus approximates to zero. If measurements of flow, volume and mouth pressure are made at short time intervals throughout the ventilatory cycle, multiple regression analysis can be used to predict $p\text{m}$ from $\dot{v}$ and v by assuming that $p\text{mus} = 0$; then coefficients of the regression equation provide estimates of R, $1/C$ and $P\text{AE}'$. If the subject is successful in keeping $p\text{mus} = 0$, the residual error waveform (the waveform of the differences between the measured and predicted value of $p\text{m}$), is small and random; therefore any structure in the waveform suggests incomplete relaxation.

Design

In figure 1B, a spring-loaded bellows has been indicated as the compliance unit because this makes an obvious analogy with the patient. However, with such an arrangement, it is difficult to achieve linearity and stability of the compliance. Also, it would be difficult to develop a method of generating a sufficiently rapidly changing *p*mus with negligible internal resistance.

A stable, linear compliance can be obtained by using the compressibility of the gas in a large rigid container, provided that the container is stuffed with sufficient suitable material to ensure that the pressure changes are isothermal [2, 17]. It is shown in the Appendix that *p*mus can then be represented indirectly by a reciprocating piston pump connected as in figure 1C and constrained to move so that the volume of gas in the pump is given by:

$$v\text{p} = -C.p\text{mus} \qquad (3)$$

Therefore, if the mechanical model of figure 1C is

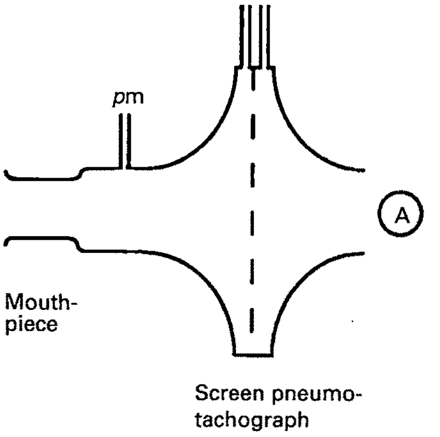

FIG. 2. Diagram of the sensing device incorporating the mouthpiece, pneumotachograph and pressure tappings. A = Connection to the ventilator breathing system, orifice resistance or atmosphere.

matched correctly to the subject in terms of compliance, resistance and *p*mus waveform, and connected to the ventilator with the same settings of the controls, the waveforms of flow, volume and mouth pressure may be expected to match those measured when the subject was connected—within the limits of validity of the conceptual model [11], the limits of accuracy of the mechanical model and the limits of reproducibility of the ventilator.

Construction

The piston pump is a modified pneumatic drive cylinder (Kay Pneumatics model No. KCL2), having a bore of 100 mm and a swept volume in excess of 1.5 litre. The piston is driven by a stepper motor (RS Components Type 34) so that one step of the motor increments or decrements the volume in the cylinder by a preset amount. The stepper motor is driven by a control board (RS Components) with a microcomputer (BBC model B) supervising its action. Digital output signals from the microcomputer control the direction of movement and step size (1 or 2 ml), and provide the train of pulses, each pulse rotating the motor one step. Therefore, by rhythmically varying the frequency and sense of the pulses, any required waveform of pump volume (*v*p) can be generated. The required waveform of *v*p is stored as an array in which each element represents the volume increment or decrement required for a time interval of 20 ms. With a step size of 1 ml, the model achieved peak flows at the "mouth" of the complete test lung in excess of 100 litre min^{-1} against a pressure of 5 kPa.

The compliance of the lung model was adjusted by combining separate, linear, rigid-container compliance units [2] (of 0.5, 0.2, 0.1 and 0.03 litre kPa^{-1} nominal value). The resistance unit of the lung model was constructed and adjusted in the manner described by Mecklenburgh [18].

EXPERIMENTAL TESTING OF THE MODEL

Measurements in the volunteer subjects

Three healthy volunteer subjects (all male, aged 27–42 yr, body mass 62–67 kg) were studied. Flow and pressure at the mouth were measured while they were breathing under five different conditions as follows:

(1) Connected to a ventilator set to provide continuous mandatory ventilation (CMV). Under this condition, the subject was instructed to relax the respiratory muscles completely. The ventilator was adjusted to match the subject in terms of frequency, but with the tidal volume set to 1.5 times his spontaneous tidal volume to reduce the urge to inspire.

(2) Breathing from atmosphere via the measuring apparatus.

(3) As condition (2), but also via an orifice plate of 7-mm diameter. This had a parabolic pressure–flow characteristic of $P = -0.52\dot{v}^2$ (approximately 0.5 kPa at 1 litre s^{-1}).

(4) Connected to the ventilator set to provide 1.0 kPa of pressure assistance.

(5) Connected to the ventilator set to deliver synchronized IMV (SIMV) at a frequency of about 5 b.p.m. and a tidal volume of 1.5 times the subject's spontaneous tidal volume.

The same ventilator, an Engström Erica II (in everyday clinical use), was used for both the subject and simulator studies, but it was serviced between these two phases of the work.

Each subject was connected to the ventilator, orifice–plate resistance, or atmosphere via a screen pneumotachograph (fig. 2). Mouth pressure was measured from a side tapping between the mouthpiece and pneumotachograph and volume was obtained by integration of the flow signal. A noseclip was used to prevent nasal breathing. The subjects were seated and care was taken to ensure that their posture was similar under all conditions.

An experiment consisted of one 4-min period of breathing under each of the five conditions, with 2-min rest periods in between, during which the subject was disconnected from the mouthpiece. Only the last 2 min of each 4-min period was recorded; this was to allow time for the breathing pattern to stabilize under each condition. These 2-min periods of recording were digitized at 20-ms intervals and stored on disc for later processing and analysis. All subjects accustomed themselves to the various loads before the experimental sequence.

The data acquisition and analysis was performed on an Apple Macintosh IIcx microcomputer equipped with an analog-to-digital input board (MIO-16, National Instruments) and running LabView software (National Instruments).

All measuring devices were calibrated before use and the calibration checked after each experiment using an RT200 Calibration Analyser (Timeter Instrument Corp., Oregon Pike, U.S.A.). The pneumotachograph was calibrated using dry air at room temperature.

It was assumed that the volume derived from integration of inspiratory flow was correct at ATP because the conditions in the pneumotachograph during inspiration were known and equivalent to the calibration conditions. However, conditions during expiration were different and unknown (and there would be some net gas exchange), so the volumes

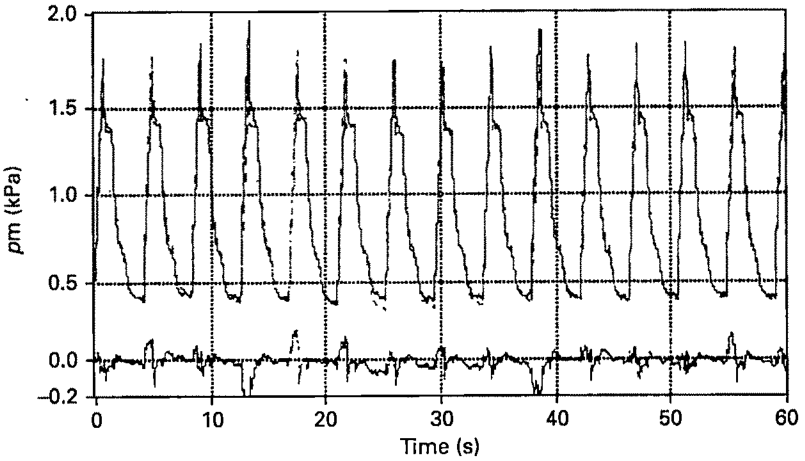

FIG. 3. Comparison of measured mouth pressure, *p*m (——), and the fitted values (– – –) obtained by the multiple-regression procedure for estimating compliance and resistance in one subject (J.M.). The lower, separate, continuous line is the difference between the two (simulated – original)—that is, the residual error. (The inadvertent 0.3 kPa of PEEP is explained in the text under "Experimental testing of the model: Simulation of the volunteer subjects with the lung model".)

TABLE I. *Compliance and resistance estimates for the three subjects and residual* SD *of* pm *about the fitted regression line. Measured values (mean (95% confidence limits)) and those used in the model*

	Compliance (litre kPa^{-1})		Resistance (kPa litre^{-1} s)		
Subject	Measured	Model	Measured	Model	Residual SD of *p*m (kPa)
J.M.	0.72 (±0.007)	0.71	0.42 (±0.026)	0.43	0.052
A.W.	0.98 (±0.029)	1.02	0.31 (±0.035)	0.33	0.080
M.H.	0.65 (±0.003)	0.61	0.38 (±0.014)	0.33	0.027

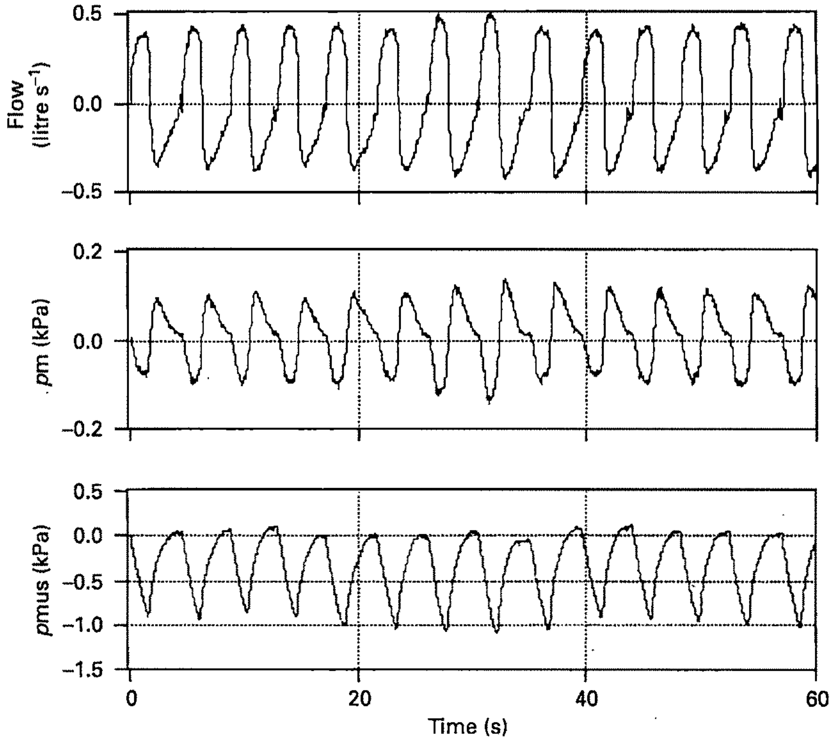

FIG. 4. Section of a typical recording from one subject (J.M.) breathing through the resistive load. The lower trace shows the *p*mus waveform calculated from the flow and mouth pressure (*p*m) waveforms, using the estimated compliance and resistance of the subject.

obtained by integration of expiratory flow were not the same as those in inspiration. This resulted in a drift of end-expiratory volume when the entire 2-min recording was integrated. It was assumed that the subjects were in a steady state and any real systematic change in end-expiratory volume caused

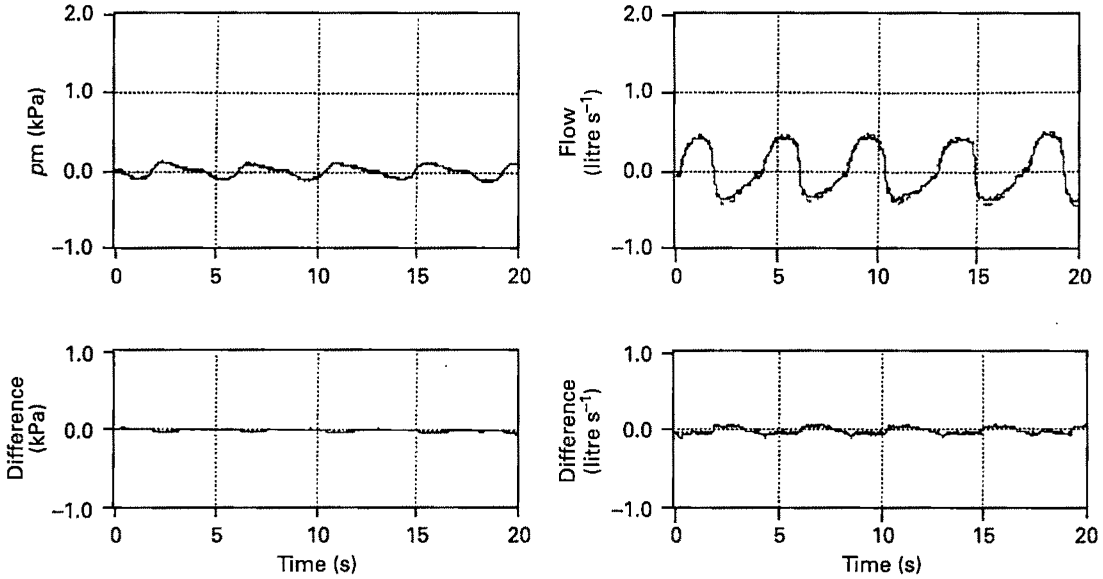

FIG. 5. Section of recordings of mouth pressure (*p*m) and flow from one subject (J.M.) breathing through the resistive load. Actual (——) and simulated (----) waveforms, together with the waveform of the difference between the two (simulated − actual).

by the introduction of a new breathing condition was complete by the start of the period of digitization. Therefore, each period of recording was truncated to include only an integral number of breaths, and an empirical calibration factor was calculated so that the drift in end-expiratory volume was eliminated over these breaths. In this way breath-to-breath variations in end-expiratory volume were preserved. After correcting expiratory flows, volume was recalculated. Thus all flows and volumes were expressed at ATP and so were directly comparable with measurements from the lung model which operated at ATP.

The data from the continuous mandatory ventilation condition were submitted to multiple regression analysis according to equation (2) (with *p*mus = 0) to determine the values of resistance and compliance. The precisions of the resistance and compliance estimates were assessed by applying the regression analysis separately to each individual breath in a 2-min recording to obtain 20–30 estimates of each parameter and calculating means and 95 % confidence limits. For the remaining conditions, *p*mus was calculated from equation (1).

Simulation of the volunteer subjects with the lung model

The model lung was set to match each subject in terms of compliance and resistance and connected in accordance with conditions (2)–(5), with the appropriate 2-min sequence of *p*mus waveform applied to the model lung. The resulting waveforms of pressure and flow at the "mouth" were compared with the corresponding pressure and flow waveforms obtained from each subject.

During the experiments with subjects, the ventilator had an inadvertent positive end-expiratory pressure (PEEP) of approximately 0.3 kPa. During the experiments with the simulator, which were performed after servicing of the ventilator, the inadvertent PEEP was absent. Therefore, to obtain equivalent conditions, the relevant control on the ventilator was set to provide an equivalent PEEP. Similarly, the pressure-assistance control was set to produce the same peak mouth pressures as in the original experiments. No immediate measurement of tidal volume was made; therefore, in SIMV with the simulator, the tidal volume control was set to the same position as for the corresponding subject.

In these simulation experiments, the composition and condition of the expired gas was the same as that of the inspired gas, so no correction was necessary except the routine correction for the slight asymmetry of the pneumotachograph output.

RESULTS

Estimates of compliance and resistance

The reliability of these estimates depends on how successful the subject is in relaxing; this is shown by how closely the fitted values of mouth pressure, from the regression analysis, match the measured values. This is illustrated for one subject in figure 3 by overlaying the measured and fitted values and by including the waveform of the difference—that is, the residual error. The magnitude of the residual error is summarized by the residual SD of the regression (the SD of the points of the error waveform in figure 3). This is given in table I for each subject, together with the mean and 95 % confidence limits of the breath-by-breath regression estimates of compliance and resistance. The values used in the lung model are given also.

Calculated pmus *waveforms*

These varied a little between subjects, between conditions and even from breath-to-breath, but always had the same, general, "curved saw-tooth" shape, as illustrated in figure 4 for one subject breathing through the resistive load.

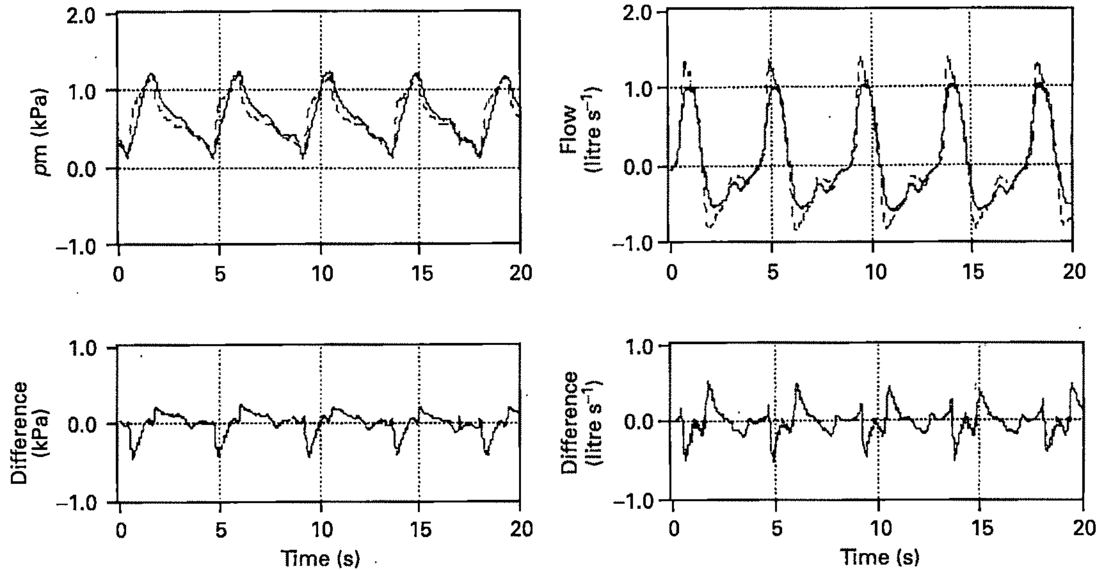

FIG. 6. Section of recordings of mouth pressure (pm) and flow from one subject (J.M.) breathing from the ventilator set to provide pressure assistance. Actual (——) and simulated (– – –) waveforms, together with the waveform of the difference between the two (simulated – actual).

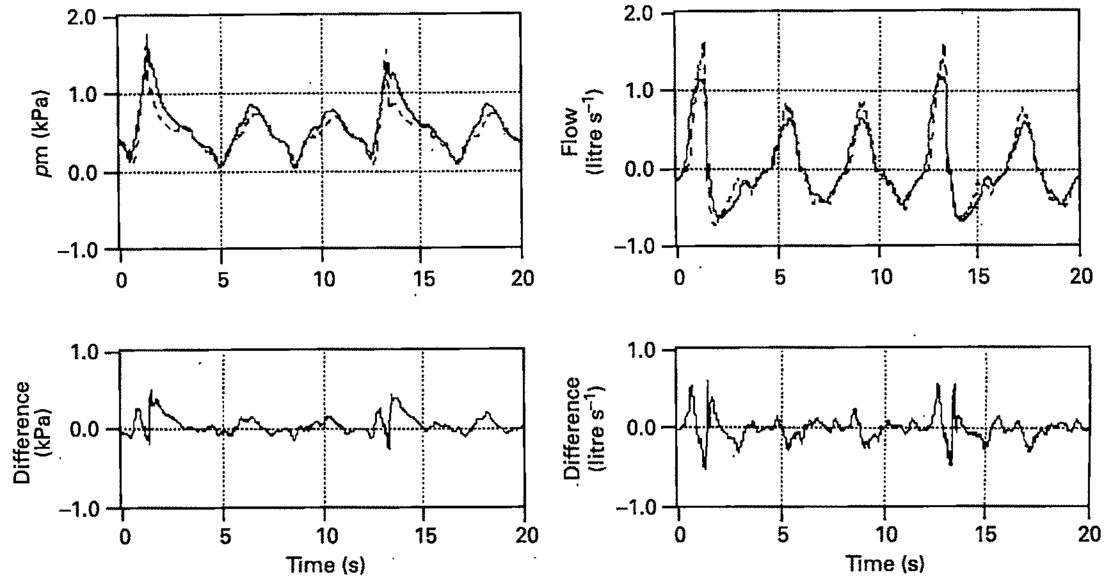

FIG. 7. Section of recordings of mouth pressure (pm) and flow from one subject (J.M.) breathing from the ventilator set to SIMV. Actual (——) and simulated (– – –) waveforms, together with the waveform of the difference between the two (simulated – actual).

Comparison of subject and simulator

The waveforms of mouth pressure and flow generated by the lung model when it was matched to each subject under each condition, were compared with the corresponding original recordings in two ways. A detailed comparison was made by overlaying the actual and simulated waveforms and also plotting the waveform of the differences. This is illustrated in figure 5 for one subject breathing through the resistive load and in figures 6 and 7 for the same subject under the pressure-assistance and SIMV conditions, respectively. A summary comparison was made in terms of the mean and SD of all the points in the difference waveforms of mouth pressure and flow (table II). (The differences between actual and simulated tidal volumes also are given in table II.) This table shows that the mean difference of mouth pressure was generally less than 0.02 kPa for breathing from atmosphere, through the resistance load or through the ventilator with pressure assistance, but this difference increased to about 0.1 kPa for the mandatory breaths in SIMV. SD values were of the order of 0.01 kPa without the ventilator and 0.1 kPa with the ventilator.

The mean differences of flow were very small indeed. SD were about 0.05 litre s^{-1} (3 litre min^{-1}) without the ventilator, 0.1 litre s^{-1} (6 litre min^{-1}) for spontaneous breaths in SIMV, and about 0.2 litre s^{-1} (12 litre min^{-1}) with pressure assistance and for the mandatory breaths in SIMV.

Mean differences of tidal volume were generally less than 0.05 litre for the conditions without the ventilatory assistance (including the spontaneous

TABLE II. *Mean* (SD) *differences between the simulated and real instantaneous values of mouth pressure and flow and between the simulated and real tidal volumes* (*simulated–real*)

	Difference in		
Condition and subject	Instantaneous mouth pressure (kPa)	Instantaneous flow (litre s^{-1})	Tidal volume (litre)
Atmosphere			
J.M.	−0.021 (0.004)	−0.0003 (0.052)	−0.048 (0.009)
A.W.	−0.011 (0.006)	0.0007 (0.070)	0.003 (0.001)
M.H.	−0.009 (0.005)	0.0004 (0.034)	0.001 (0.003)
Mean	−0.014 (0.005)	0.0003 (0.051)	−0.014 (0.004)
Resistance			
J.M.	−0.012 (0.015)	0.0006 (0.044)	0.058 (0.006)
A.W.	−0.022 (0.013)	0.0002 (0.052)	0.026 (0.010)
M.H.	−0.011 (0.010)	0.0003 (0.037)	0.019 (0.005)
Mean	−0.015 (0.013)	0.0004 (0.044)	0.034 (0.007)
Pressure assistance			
J.M.	−0.012 (0.121)	0.0020 (0.172)	0.134 (0.011)
A.W.	−0.017 (0.114)	0.0008 (0.233)	0.125 (0.012)
M.H.	−0.017 (0.115)	0.0001 (0.157)	0.057 (0.014)
Mean	−0.016 (0.116)	0.0010 (0.187)	0.105 (0.012)
SIMV (spontaneous breaths)			
J.M.	−0.033 (0.091)	0.0045 (0.101)	0.071 (0.027)
A.W.	−0.027 (0.053)	0.0001 (0.125)	0.077 (0.039)
M.H.	−0.068 (0.089)	−0.0004 (0.099)	−0.029 (0.012)
Mean	−0.043 (0.078)	0.0014 (0.108)	0.039 (0.026)
SIMV (mandatory breaths)			
J.M.	−0.109 (0.151)	−0.0104 (0.205)	−0.097 (0.013)
A.W.	−0.094 (0.150)	−0.0038 (0.254)	−0.068 (0.096)
M.H.	−0.094 (0.162)	0.0024 (0.247)	−0.076 (0.011)
Mean	−0.099 (0.154)	0.0030 (0.235)	−0.080 (0.040)

breaths in SIMV), but the differences increased to about 0.1 litre for the mandatory breaths in SIMV and for pressure assistance. The SD values of the differences of tidal volume were mostly around 0.01 litre for all conditions, except for one subject (A.W.) during SIMV.

DISCUSSION

In the determination of the compliance and resistance of each subject, some incompleteness of relaxation is indicated by the structure in the waveform of the difference between measured and fitted *p*m (fig. 3). However, even in the least relaxed subject (A.W.) the residual SD amounted to only 8% of the 1 kPa peak-to-peak variation of *p*m (table I). In this subject, the 95% confidence limits of the compliance and resistance estimates were 3% and 11% of the means, respectively, whilst for the other subjects these were less than 1% and about 5%, respectively. This seems adequate precision for a simple, two-component, compliance-and-resistance representation of the total respiratory impedance. When non-linear compliance and resistance terms and an inertance term were included in the regression equation the fit improved, but not sufficiently to justify the complication of representing these additional terms in the lung model.

The *p*mus waveform was similar in different individuals and under different conditions. The typical waveform (fig. 4) was predominantly a negative pressure deflection that started rapidly and had a brief negative peak and a roughly exponential decay, although the final value was often either slightly positive or negative. This might be attributed to variation in resting muscle tone and explain the variation in FRC between breaths. When the waveforms are plotted on a faster time base (fig. 8) it can be seen that *p*mus does not return towards zero until well after expiratory flow has commenced; the inspiratory muscles relax gradually, controlling the changeover to expiratory flow and the early part of expiration. The reversal of flow occurs when the magnitude of *p*mus has decreased to less than the recoil pressure of the lungs and chest wall.

The model was able to reproduce faithfully the breathing pattern of our volunteers. This is shown by the smallness of the differences between the volunteer and simulation recordings of pressure and flow at the mouth for breathing from atmosphere and through the resistance; table II indicates that figure 5 is typical of all three subjects breathing through the resistance or from atmosphere.

When the subjects were breathing from the ventilator with pressure assistance, the mean differences between real and simulation values for mouth pressure and flow were similar to the preceding conditions, but the SD of the instantaneous differences increased generally to about 12% of the peak-to-peak amplitudes. For tidal volume, the SD of the difference between breaths was about 1.5% of the mean tidal volume (0.8 litre). This indicates consistency, but the mean simulation tidal volume was nearly 150 ml too large in two subjects. Examination of figure 6, which shows a section of real and simulation recording under pressure assistance, reveals that the maximum and minimum values of *p*m, as intended, were similar for volunteer and simulation, but the mouth pressure consistently increased and decreased more rapidly in the simulation than in the original recording, leading to larger peak flows in both directions and hence larger tidal

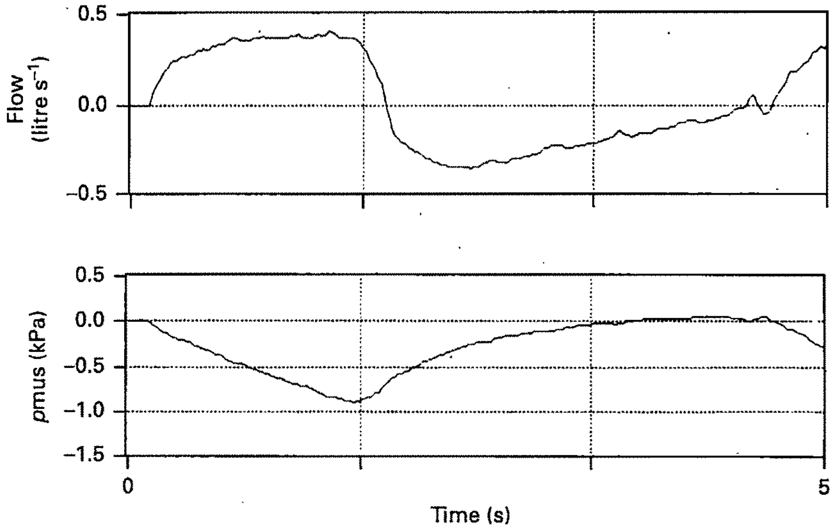

FIG. 8. A section of flow and *p*mus waveform from the recording in figure 4 displayed on a fast time base to show that flow does not reverse from the inspiratory to the expiratory direction until the *p*mus waveform has returned part of the way towards 0, and that *p*mus does not become 0 until some time after expiratory flow starts.

volumes. In the pressure-assistance mode, mouth pressure during the inspiratory phase was much more dependent on the ventilator than the subject. We therefore suggest that the rapid increase and decrease in mouth pressure (and hence increased tidal volume) in the simulation is the result of the servicing that occurred between the real and simulation recordings.

During SIMV, it appeared that the simulation of the flow and mouth pressure waveforms was quite good for the spontaneous breaths, but notably poorer for the mandatory breaths (fig. 7, table II). This difference between spontaneous and mandatory breaths was noticeable also in the tidal volume differences between volunteer and simulation (table II). Here the explanation may be that, although the volume control of the ventilator was set to the same position in the simulation experiment as in the original experiment, a small change in calibration of the control occurred during servicing.

Close inspection of the flow waveform in figure 7 shows also that the synchronized mandatory breaths in the simulation recording started slightly later and were of shorter duration than in the volunteer recording. This produced a large transient error in flow at the start of the synchronized mandatory breath. This difference in duration of the inspiratory phase of the ventilator could, as before, be a result of inaccuracy of setting or different calibration of the controls of the ventilator following servicing, whilst the delayed start could be a change in triggering performance.

Despite these differences of detail, the simulation is faithful qualitatively, and the differences are not large quantitatively: generally less than 5% with passive loads and less than 10% with the ventilator after servicing. This is much better than in previous models with which gross discrepancies have occurred when the simulated patient and ventilator were both flow generators (or the ventilator a high-pressure ventilator). For instance, in an earlier study from this department [4] we vented excess flow during mandatory breaths from the ventilator and ignored such breaths as being unrepresentative. Oh, Lin and Bhatt [7], in testing the Siemens Servo 900c ventilator, did not have a spill and large pressure transients were noticeable in the inspiratory phase. When we mimicked these tests with our model, there were no large pressure transients. It is our contention that the pressure transients were a consequence of the model of Oh and associates not having a realistic compliance during the inspiratory phase.

Two models have been described that incorporate realistic lung mechanics, but with flow-generating simulated spontaneous activity. In the model of Lyle and colleagues [5], as soon as the delivered flow from the ventilator exceeds the flow required by the spontaneous breath, the active part of the model is disabled, leaving only the compliance and resistance components operative. In the model of Damia and colleagues [6] a compliance element is incorporated, together with a flow generator which is intended to match the waveform of inspiratory flow. However, in their model, the compliance is operative only for positive alveolar pressure and is closed off during the inspiratory phases.

The mechanical forms of both these models could be brought into conformity with our conceptual model if they were modified sufficiently. In the model of Damia and others [6] this would require that the diaphragm-type compliance unit should operate throughout the ventilatory cycle and have a linear pressure–volume relationship for the full range of positive and negative pressures encountered, and for the bellows to be moved according to a waveform of *C.p*mus instead of a waveform of flow at the mouth. Here the difficulty would be in producing constant compliance in a diaphragm-type compliance unit. In the model of Lyle and others [5], it would be necessary to apply a waveform of *p*mus to the driving ("spontaneous") bellows and link this permanently (instead of conditionally) to the "patient" bellows. Here, in addition to the difficulty in obtaining constant compliance, there would also be the problem of generating the required waveform of pressure.

We conclude that our method of using a pressure equivalent to the respiratory muscle activity ($p\mathrm{mus}$) to drive a model lung, having realistic compliance and resistance values, can simulate accurately the interaction between a particular patient and a particular passive load, or a particular setting of a particular ventilator. We think that the greater discrepancies found with the ventilator than with the passive load may fairly be attributed to the setting and performance of the ventilator being not quite the same as in the original experiment. In other words, we were already effectively using the model to test the performance of a ventilator.

We are now investigating the variation of the $p\mathrm{mus}$ waveform between subjects and between conditions in order to verify a suitable "standard" waveform or waveforms for the comparative testing of ventilators [12].

APPENDIX

CALCULATION OF $p$mus AND ITS SIMULATION IN THE MODEL LUNG

The analysis below uses the convention of upper case symbols for parameters and lower case for instantaneous values of variables. All pressures are expressed as differences from ambient atmospheric pressure.

Let total respiratory compliance, C, be defined as the increase, Δv, in the volume of contained gas (at ATP) per unit increase in the pressure difference, Δp, across the wall of the compliance. Then, during passive inflation (no respiratory muscle activity in figure 1A, or $p\mathrm{mus} = 0$ in figure 1B):

$$C = \frac{\Delta v}{\Delta p\mathrm{A}}$$

where $p\mathrm{A}$ is the alveolar pressure (or pressure in the compliance unit—not quite the same as alveolar pressure because it is separated from the "mouth" by the total respiratory resistance instead of only the airways resistance). Hence:

$$\Delta v = C.\Delta p\mathrm{A} \qquad \text{(A1)}$$

During spontaneous breathing ($p\mathrm{mus}$ varying in figure 1B):

$$\begin{aligned}\Delta v &= C.\Delta(p\mathrm{A} - p\mathrm{mus})\\ &= C.\Delta p\mathrm{A} - C.\Delta p\mathrm{mus} \qquad \text{(A2)}\end{aligned}$$

In this study volume, v, added to the lungs was obtained by integration from a start of inspiratory flow – that is, from the end of an expiratory phase. Let the values of $p\mathrm{A}$ and $p\mathrm{mus}$ at that time be $P\mathrm{AE}'$ and $P\mathrm{musE}'$. Then:

$$v = C(p\mathrm{A} - P\mathrm{AE}') - C(p\mathrm{mus} - P\mathrm{musE}') \qquad \text{(A3)}$$

At any instant

$$p\mathrm{m} = p\mathrm{A} + R.\dot{v} \qquad \text{(A4)}$$

where R = total respiratory resistance and $\dot{v}$ = flow (inspiratory direction positive).

Eliminating $p\mathrm{A}$ from equations (A3) and (A4) gives

$$p\mathrm{mus} - P\mathrm{musE}' = p\mathrm{m} - R\dot{v} - \frac{v}{C} - P\mathrm{AE}' \qquad \text{(A5)}$$

Unless the expiratory muscles are used, it can reasonably be assumed that $P\mathrm{musE}' = 0$ (apart from some small random variation in end-expiratory muscle tone). In these circumstances, the equation simplifies to:

$$p\mathrm{mus} = p\mathrm{m} - R.\dot{v} - \frac{v}{C} - P\mathrm{AE}' \qquad \text{(A6)}$$

It can be seen from equation (A4) that $P\mathrm{AE}'$ can be determined from the value of $p\mathrm{m}$ when $\dot{v} = 0$ (at the change-over from expiration to inspiration). Therefore, if R and C are known and $p\mathrm{m}$, $\dot{v}$ and v are monitored, $p\mathrm{mus}$ can be computed.

In practice, it is simpler to rewrite the more general equation (A5) as:

$$p\mathrm{mus} - (P\mathrm{musE}' - P\mathrm{AE}') = p\mathrm{m} - R.\dot{v} - \frac{v}{C} \qquad \text{(A7)}$$

and to compute $p\mathrm{mus} - (P\mathrm{musE}' - P\mathrm{AE}')$. Even when the expiratory muscles are in use, so that $P\mathrm{musE}'$ is not zero, $P\mathrm{musE}'$ and $P\mathrm{AE}'$ are still constants (the values of $p\mathrm{mus}$ and $p\mathrm{A}$ at the instant that integration started). Therefore equation (A7) is a universal means of determining the shape of the waveform of $p\mathrm{mus}$, but not the position of its zero. When, as in the present study, the expiratory muscles are not being used, the zero can be assumed to be at the mean of the end-expiratory values of the $p\mathrm{mus}$ waveform.

Simulation

During passive inflation, the compliance of the respiratory system determines the volume–pressure (v–$p\mathrm{A}$) relationship in the lungs according to equation (A1). Subject to that relationship, the pressure or flow generator in the ventilator (and the impedances of the breathing system and patient's respiratory system) determine how v and $p\mathrm{A}$ (and $\dot{v}$ and $p\mathrm{m}$) vary with time during the ventilatory cycle.

When spontaneous ventilation occurs, the v–$p\mathrm{A}$ relationship is changed to that of equation (A2) but, subject to this new relationship (which varies with time as $p\mathrm{mus}$ varies), the ventilator again determines how v, $p\mathrm{A}$, $\dot{v}$ and $p\mathrm{m}$ vary. Therefore, if the realized model of figure 1C can be made to produce the same, time-varying, v–$p\mathrm{A}$ relationship as applies in figure 1B (A2), the same variation (the same waveforms, of v, $p\mathrm{A}$, $\dot{v}$ and $p\mathrm{m}$) will be produced when the model is connected to the same ventilator with the same settings—or to any other specified load.

In figure 1C, there is no $p\mathrm{mus}$ as such, but some of the volume added to the lungs goes into the pump. Therefore, equation (A1) becomes:

$$\Delta v - \Delta v\mathrm{p} = C.\Delta p\mathrm{A}$$

or

$$\Delta v = C.\Delta p\mathrm{A} + \Delta v\mathrm{p} \qquad \text{(A8)}$$

where $\Delta v\mathrm{p}$ is the change in the volume of gas (at ATP) in the pump. Therefore, comparing (A8) with (A2) shows that if, in any time interval

$$\Delta v\mathrm{p} = -C.\Delta p\mathrm{mus},$$

the relationship between Δv and $\Delta p\mathrm{A}$ will be the same as in the direct model (fig. 1B).

More specifically, if the volume added to the lungs, and the volume in the pump, $v\mathrm{p}$, are expressed relative to the volumes at the start of the simulation, and if $P\mathrm{A}_0$ is the value of $p\mathrm{A}$ at that time, (A8) becomes:

$$v = C(p\mathrm{A} - P\mathrm{A}_0) + v\mathrm{p} \qquad \text{(A9)}$$

Comparing this with (A2) shows that, if $v\mathrm{p}$ is made continuously equal to $-C$ ($p\mathrm{mus} - P\mathrm{musE}'$) calculated for a given volunteer experiment, and $P\mathrm{A}_0$ is set equal to the corresponding $P\mathrm{AE}'$, the relationship between v and $p\mathrm{A}$ will be exactly the same as in the volunteer experiment. In practice it is not necessary to set $P\mathrm{A}_0$ in the simulator because it can be anticipated that any discrepancy in the initial conditions will die out over a few breaths. This is because the average end-expiratory $p\mathrm{A}$ is what is needed to ensure no trend in end-expiratory volume in the lungs—that is, equal inspiratory and expiratory tidal volumes on average, both in the simulation and in the volunteer experiment (given the corrections used). Finally, as in the volunteer experiments it was reasonable to assume that $p\mathrm{musE}'$ was equal to zero, the requirement for equivalence becomes just:

$$v\mathrm{p} = -C.p\mathrm{mus} \qquad \text{(A10)}$$

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THE ANTIOXIDANT POTENTIAL OF PROPOFOL (2,6-DIISOPROPYLPHENOL)†

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SUMMARY

We have examined in vitro *the antioxidant properties of 2,6-diisopropylphenol. In studies using electron spin resonance spectroscopy we have demonstrated that 2,6-diisopropylphenol acts as an antioxidant by reacting with free radicals to form a phenoxyl radical—a property common to all phenol-based free radical scavengers. In additional experiments, the antioxidant properties of the clinical formulation of 2,6-diisopropylphenol (propofol) have been measured using an assay of antioxidant potential. In these experiments, propofol, but not Intralipid, was found to exhibit significant antioxidant activity, such that in the range of propofol concentrations examined (10^{-6}–10^{-5} mol litre^{-1}), each molecule of 2,6-diisopropylphenol was able to scavenge two radical species. We conclude that the free radical scavenging properties of 2,6-diisopropylphenol resemble those of the endogenous antioxidant α-tocopherol (vitamin E).*

KEY WORDS

Anaesthetics, intravenous: propofol, antioxidant potential.

Free radicals are believed to contribute to the tissue injury associated with a wide range of acute and chronic conditions [1]. Of particular interest to the anaesthetist and intensive therapist are reperfusion injury and acute inflammatory processes such as acute lung injury, severe sepsis and multisystem organ failure [2]. Free radical scavengers, or antioxidants, represent an important component of the body's defences against such free radical mediated injury, so that boosting of these defences may emerge as an important therapeutic aim. Although specific antioxidant therapies are still at the experimental stage, several drugs are already available which, incidental to their major biological action, may augment free radical scavenging capacity. This group of drugs includes salicylates [3] and barbiturates [4], although the clinical value of such properties is uncertain.

Propofol, the currently available formulation of the anaesthetic agent 2,6-diisopropylphenol, has been shown to attenuate experimental reperfusion injury in the cerebral cortex [5], although the mechanism underlying this action has yet to be defined. Oxygen-derived free radicals may contribute to such injury, and as propofol is chemically similar to phenol-based free radical scavengers such as butylated hydroxytoluene (BHT) and the endogenous antioxidant vitamin E (fig. 1) [1], we have examined the hypothesis that propofol is a free radical scavenger.

Phenol-based antioxidants (R-OH) scavenge free radical species (X·) by a process of hydrogen abstraction, and thereby themselves become a (less reactive) phenoxyl radical (R-O·):

$$\text{R-OH} + \text{X}\cdot \rightarrow \text{R-O}\cdot + \text{XH}$$

In order to examine the hypothesis that propofol behaves in a similar way, we have used electron spin resonance (ESR) spectroscopy, one of the more specific methods of characterizing radical reactions [1], to examine the way in which propofol reacts with free radical species, and in particular to identify if a propofol-derived phenoxyl radical is generated under such conditions.

Lipid peroxidation is a free radical-mediated chain reaction [1]. In the second part of this *in vitro* study we have measured the free radical scavenging capacity of propofol by comparing its ability to arrest lipid peroxidation with that of an established free radical scavenger of known potency.

METHODS

In vitro *investigation of the oxidation of propofol*

As noted above, the chemical similarities between 2,6-diisopropylphenol and phenol-based antioxidants suggest that, after oxidation by a free radical species, it should become a phenoxyl radical. This hypothesis was tested in two parts.

The first experiments were designed to define the ESR spectrum of the oxidation product of 2,6-diisopropylphenol (the propofol phenoxyl radical). The limited aqueous solubility of this material required that these experiments were performed both using a saturated solution of 2,6-diisopropylphenol (Sigma) dissolved in a 2:1 mixture of water and acetone, and on the clinical formulation of the

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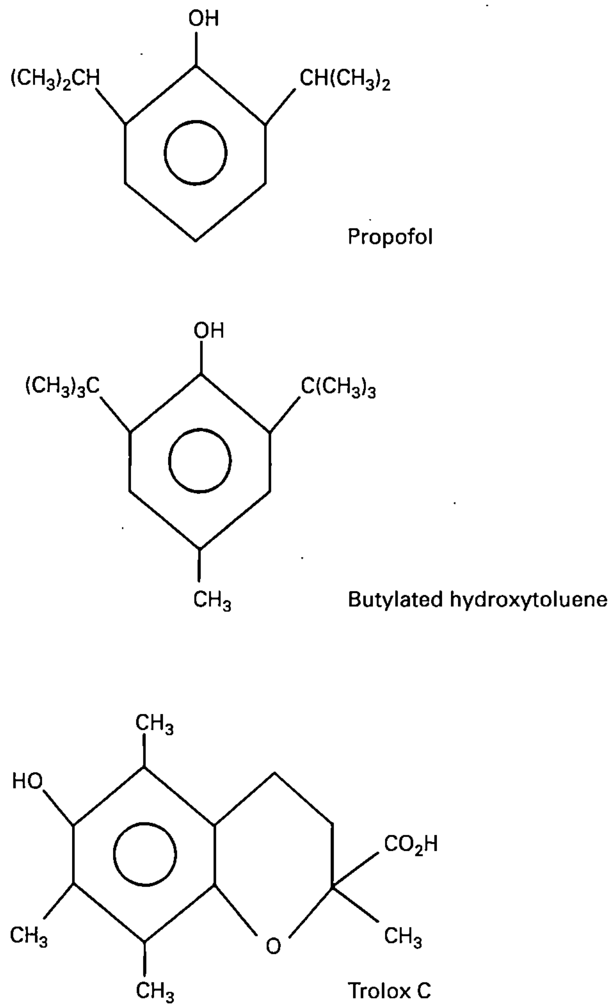


FIG. 1. Structural formulae of 2,6-diisopropylphenol (propofol), butylated hydroxytoluene (BHT) and Trolox C (a water soluble analogue of vitamin E). All three compounds carry a hydroxyl substituent on their phenol rings, which is known to confer free radical scavenging properties on both BHT and Trolox C.

compound—propofol. Oxidation was carried out with potassium permanganate 1 mmol litre^{-1} (pH range 9.5–11.5), using a two-stream rapid mixing system as described previously [6, 7]. ESR spectra of the reaction mixtures were recorded at room temperature using a Bruker ESP 300 ESR spectrometer equipped with 100-kHz modulation and a Bruker ER035M gaussmeter for field calibration. We measured directly from the field scan the hyperfine coupling constants characterizing the radicals which were detected.

When the nature of the propofol phenoxyl radical had been identified, additional experiments were designed to investigate if the same species was produced when propofol was exposed to radical generating systems—that is, to identify if propofol was able to scavenge these radicals. Two radical generating systems were used: a mixture of haematin 250 μmol litre^{-1} and butyl hydroperoxide (^{t}BuOOH) 3.5 mmol litre^{-1}, which generates peroxyl and alkoxyl radicals, and a hydroxyl radical (OH·) generating system consisting of titanium triiodide 8 mmol litre^{-1} and hydrogen peroxide 33 mmol litre^{-1}. These were applied to three preparations of 2,6-diisopropylphenol (all at pH 7): a saturated aqueous solution of 2,6-diisopropylphenol; a saturated solution of 2,6-diisopropylphenol in a 2:1 mixture of water and acetone, and the clinical formulation of propofol; the reactions were examined under the same ESR conditions as defined above, but with the use of a three-stream rather than two-stream rapid mixing system [8].

In vitro *measurement of antioxidant potential*

We have investigated the ability of propofol to arrest lipid peroxidation using the Total Radical Antioxidant Potential (TRAP) assay [9]. This is an assay of the antioxidant activity of plasma, which is obtained by comparing the duration of time for which plasma is able to resist lipid peroxidation with that achieved after addition of a known amount of an established antioxidant—in this case Trolox C (6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid (fig. 1)), a water soluble analogue of vitamin E. Lipid peroxidation was initiated by adding a small quantity of a water soluble azo compound 2,2-azo-bis-(2-amidinopropane) (ABAP) to a sample of diluted plasma. As lipid peroxidation is an oxygen consuming reaction, the rate of peroxidation was estimated by following changes in the oxygen tension ($P\mathrm{O}_2$) in the reaction chamber with time. Initially, antioxidants present within the plasma limit the rate of peroxidation, but as they are consumed by the scavenging process, lipid peroxidation is able to take place more readily. A plot of the change in $P\mathrm{O}_2$ of the system with time (fig. 2) thus shows a gradual increase in the rate of decline of oxygen tension as the free radical-mediated oxygen-consuming reactions are able to take place at an increasing rate. The peroxidation reactions can be inhibited by adding exogenous antioxidant to the system (in these experiments, Trolox C), but this effect too is only temporary, after which the rate of oxygen consumption once again increases. As displayed in figure 2 by fitting tangents to those parts of the $P\mathrm{O}_2$–time curves where the rate of change in $P\mathrm{O}_2$ is at its least (immediately after the addition of ABAP or Trolox C) and at its greatest (when all available antioxidants have been consumed), these plots are used to derive graphically the "induction" times for plasma and Trolox C, τ_{P} and τ_{Tr} respectively. These induction times were then used to quantify the antioxidant activity of the plasma in terms of a molar TRAP value, which is calculated from the equation:

$$\mathrm{TRAP} = \frac{n[\mathrm{Trolox}].\tau_{\mathrm{P}}}{f.\tau_{\mathrm{Tr}}}$$

where n is the number of radicals trapped per molecule of Trolox (= 2), and f is a factor which allows for the dilution of the plasma. Although the fitting of the tangents introduces a subjective element to the method, the results from this technique correspond well with a more objective but technically more demanding assay of plasma antioxidant potential [9].

Measurement of plasma TRAP. Changes in oxygen tension in the reaction system were monitored using a Rank oxygen electrode (Rank Brothers, Bottisham, Cambridge), with the Clark-type electrode mounted in the base of a reaction cell and maintained at 37 °C

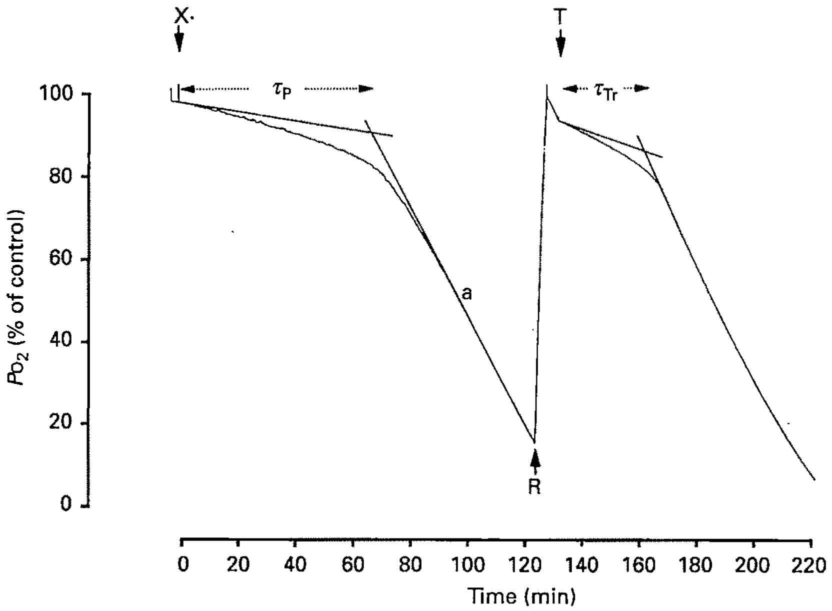


FIG. 2. Changes in oxygen tension (Po_2) with time observed using the TRAP assay of plasma antioxidant capacity. ABAP (X·) was added to initiate lipid peroxidation. At a, the rate of decrease in Po_2 reached a maximum as a result of consumption of available antioxidants in the system and consequent increase in the rate of (oxygen consuming) lipid peroxidation. Following partial reoxygenation (R), the addition of 25 µl of Trolox C 0.4 mmol litre^{-1} (T) temporarily arrested these reactions, so that the rate of oxygen consumption slowed again. The induction periods for plasma and Trolox C (τ_P and τ_{Tr}, respectively) were derived graphically by fitting tangents to the shallowest and steepest extreme of the appropriate Po_2–time curve. The total radical antioxidant potential (TRAP) value for the plasma was calculated from the ratio of the two induction periods.

with a heated water jacket. Thirty microlitre of ABAP 0.4 mol litre^{-1} (Polysciences) was added to 3 ml of aerated, prewarmed phosphate buffered saline 10 mmol litre^{-1} (Sigma). Fresh plasma (100-µl aliquots) donated on the day of the experiments by healthy, non-fasted human volunteers, was vortex mixed with 99% linoleic acid 9 µl (antioxidant free, Sigma) for 30 s and 50 µl of the resulting mixture added to the cell. Linoleic acid was stored in the dark at −40 °C under nitrogen, and used within 1 week. After completion of the plasma induction period, the cell was re-oxygenated before adding 25 µl of Trolox C 0.4 mmol litre^{-1} (Aldrich).

Measurement of the antioxidant capacity of propofol. The ability of propofol to arrest lipid peroxidation in this system was assessed in two ways. In the first series of experiments, after measurement of plasma TRAP as described above, propofol (the clinical formulation of 2,6-diisopropylphenol in 10% Intralipid: Diprivan, ICI) was added to the *in vitro* system in the same way as Trolox C. The effect of propofol was examined at three different concentrations (1×10^{-6} mol litre^{-1}, 5×10^{-6} mol litre^{-1} and 1×10^{-5} mol litre^{-1}; $n = 8$ in each case), whilst in parallel control experiments the effect of equivalent amounts of Intralipid (10% Intralipid solution, KabiVitrum) was determined. Induction times for Trolox C and propofol were then derived from the plots of Po_2 against time at these three propofol concentrations. As it is known that each molecule of Trolox C traps two radicals produced in this system ($n_{Tr} = 2$), these data were used to calculate a similar value for propofol, according to the equation:

$$n_{prop} = n_{Tr} \cdot \left(\frac{C_{Tr}}{C_{prop}}\right) \cdot \left(\frac{\tau_{prop}}{\tau_{Tr}}\right)$$

where C_{prop} and C_{Tr} are the concentrations of propofol and Trolox C, respectively, and τ_{prop} is the induction time for propofol.

In a second series of experiments, the contribution made by propofol to plasma antioxidant capacity was examined. Propofol was added to plasma obtained from healthy human volunteers to produce a concentration of 20 µg ml^{-1}, parallel control samples of plasma receiving equivalent volumes of Intralipid. The TRAP values for the two groups of samples were measured and the difference between the two groups taken to represent the contribution made by 2,6-diisopropylphenol to the antioxidant capacity of the plasma.

Statistical analysis

Where appropriate, values are expressed as mean (SEM). Statistical significance was assessed using Student's unpaired *t* test and accepted when $P < 0.05$. Significant differences were quantified by confidence interval analysis and expressed in terms of 95% confidence intervals of the difference of the mean.

RESULTS

ESR studies

Essentially identical ESR spectra were generated from the oxidation of 2,6-diisopropylphenol and propofol by potassium permanganate (fig. 3), although baseline noise was greater in the propofol experiments, presumably as a result of the presence of lipid. The parameters of this radical species (a_H 0.966, a_{2H} 0.344 and a_{2H} 0.172 mT) are consistent with the appearance of a phenoxyl radical following oxidation [10].

Weak spectra of the phenoxyl radical species identified above were detected after exposure of a

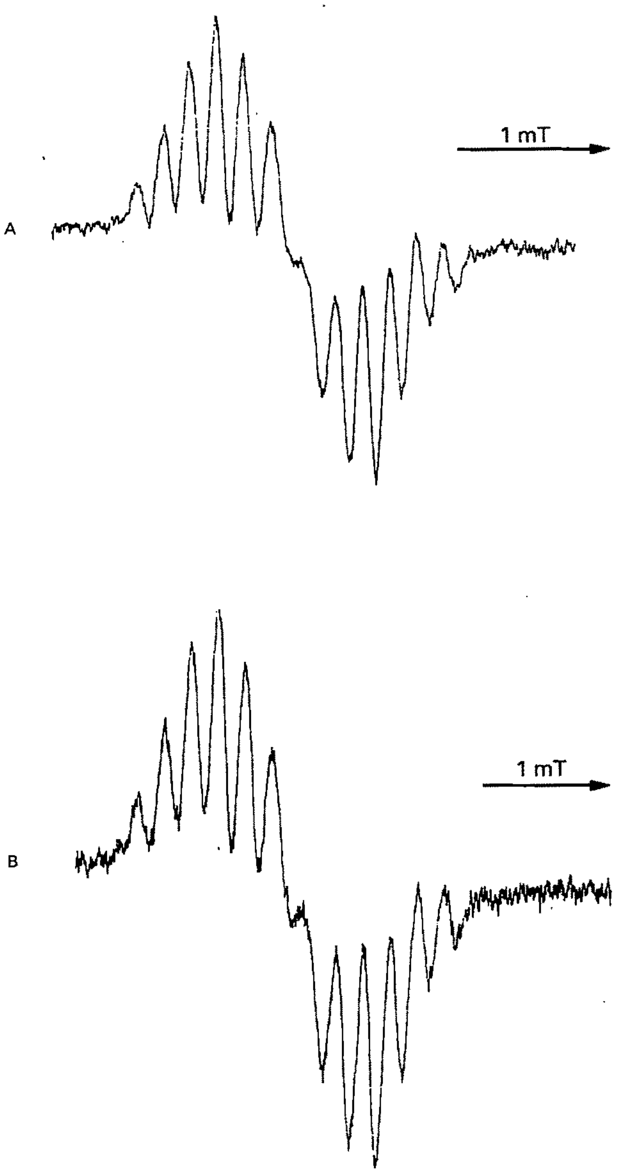


FIG. 3. Electron spin resonance (ESR) spectra of 2,6-diisopropylphenol adducts produced by the oxidation of a saturated solution of 2,6-diisopropylphenol in a 2:1 mixture of water and acetone (A) and propofol (B) with potassium permanganate 1 mmol litre^{-1}. The ESR characteristics of this radical identify it as a phenoxyl species. Gain 1×10^6 in each case; baseline noise greater in propofol spectrum as a result of the presence of lipid.

saturated solution of 2,6-diisopropylphenol in water–acetone to the haematin–^{t}BuOOH system, suggesting that 2,6-diisopropylphenol can scavenge peroxyl and alkoxyl radicals. The presence of lipid, however, interfered with parallel experiments using propofol. In the experiments using the titanium–hydrogen peroxide system, OH· appeared to react preferentially with the acetone or lipid solvents, while in experiments using the aqueous preparation the solubility of 2,6-diisopropylphenol was so poor that the small concentrations of radical produced were insufficient to allow ESR detection.

Antioxidant capacity of propofol

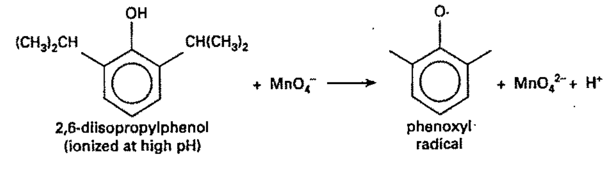
Comparison of the antioxidant potencies of propofol, Intralipid and Trolox C. Equivalent amounts of both Trolox C and propofol were able to decrease the rate of oxygen consumption (and therefore the rate of lipid peroxidation) to approximately the same extent in the TRAP assay system whilst, in contrast, the addition of an equivalent amount of Intralipid had no effect (fig. 4).

The induction times for the three concentrations of propofol examined are shown in table I, together with the corresponding induction times for Trolox C. As expected, the induction period for propofol, τ_{prop}, increased in proportion to the concentration of propofol used. The antioxidant potency of propofol, n_{prop}, was similar across the range of concentrations studied: 1.9 (SEM 0.1), 2.2 (0.1) and 2.1 (0.1) at 1×10^{-6}, 5×10^{-6} and 1×10^{-5} mol litre^{-1}, respectively.

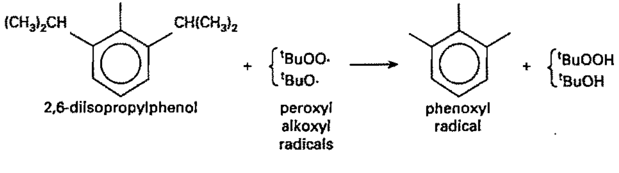
Effect of propofol on plasma TRAP. The addition of propofol to human plasma significantly increased the plasma antioxidant capacity. Thus the TRAP value measured for propofol-treated plasma was significantly greater than that after addition of Intralipid (1238 (30) μmol litre^{-1} compared with 1023 (27) μmol litre^{-1}, respectively; 95% confidence interval of the difference = 130–301 ($P < 0.0001$)).

DISCUSSION

Vitamin E is an important endogenous cell membrane antioxidant, while BHT is an established free radical scavenger used widely as a food additive to prevent rancidification of fats [1]. The chemical similarities between these phenol-based antioxidants and 2,6-diisopropylphenol suggest that the latter may behave in a similar fashion. ESR spectroscopy is a powerful tool for characterizing the nature of radical reactions, and has been used in this study first to confirm that 2,6-diisopropylphenol indeed becomes a phenoxyl radical when oxidized by permanganate:



Definition of the ESR spectrum of this phenoxyl species then allowed us to test the hypothesis that 2,6-diisopropylphenol was able to act as a free radical scavenger by looking for its production when the agent was exposed to radical generating systems. Identification of this species when 2,6-diisopropylphenol was exposed to a peroxyl–alkoxyl radical generating system (haematin–^{t}BuOOH) confirmed this hypothesis:



Failure to demonstrate a similar effect when 2,6-diisopropylphenol was exposed to hydroxyl radicals

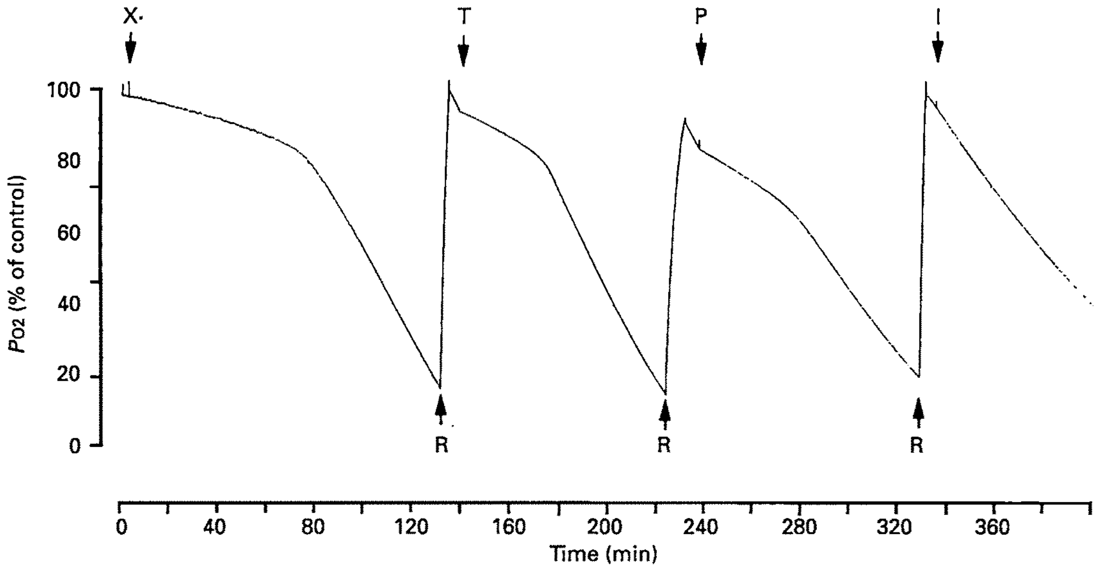


FIG. 4. Effects of Trolox C (T), propofol (P) and Intralipid (I) on the rate of oxygen consumption in the TRAP assay system. Trolox C and propofol (3.3×10^{-6} mol litre^{-1} in each case) arrested oxygen consumption (and so lipid peroxidation) to the same extent. In contrast, an equivalent amount of 10% Intralipid was without effect. X· = ABAP; R = reoxygenation.

TABLE I. *The antioxidant potency of propofol in the TRAP assay system. The mean (SEM) number of radicals scavenged per molecule of propofol (n_{prop}) is calculated from the ratio of the graphically derived induction periods for Trolox C and propofol (τ_{Tr} and τ_{prop}, respectively). The effect of propofol was examined at three different concentrations (1×10^{-6}, 5×10^{-6} and 1×10^{-5} mol litre^{-1}) and compared with a standard Trolox C concentration (3.3×10^{-6} mol litre^{-1})*

	Propofol concentration (mol litre^{-1})		
	1×10^{-6}	5×10^{-6}	1×10^{-5}
τ_{Tr} (min)	31.3 (0.7)	31.3 (0.6)	27.5 (1.7)
τ_{prop} (min)	8.9 (0.3)	52.1 (1.3)	85.0 (3.1)
n_{prop} (No.)	1.9 (0.1)	2.2 (0.1)	2.1 (0.1)

was disappointing, but not surprising, with the hydroxyl radical reacting preferentially with the large concentrations of acetone present as a solvent. In much the same way, as free radicals are known to react with lipid, it is no surprise that parallel experiments using the clinical formulation propofol were inconclusive. Nevertheless, these ESR spectroscopic studies have served to establish qualitatively the nature of the possible interaction between 2,6-diisopropylphenol and free radicals.

In the second part of the study, we have attempted to quantify the antioxidant potency of 2,6-diisopropylphenol by examining its ability to limit lipid peroxidation. The demonstration that propofol, but not Intralipid, arrested oxygen consumption in the TRAP assay supports the hypothesis that 2,6-diisopropylphenol is a free radical scavenger, and we would propose that it interferes with lipid peroxidation in the following way. Lipid peroxidation is initiated according to the reaction:

$$LH + X\cdot \rightarrow L\cdot + XH$$

in which a radical X· (such as the carbon-centered radical generated by ABAP) abstracts a hydrogen atom from lipid (LH) to produce an intermediate lipid radical (L·). This radical is able to combine with molecular oxygen to form a lipid peroxyl radical (L-OO·), which is capable of abstracting a hydrogen atom from another lipid molecule:

$$L\cdot + O_2 \rightarrow L\text{-}OO\cdot$$
$$L\text{-}OO\cdot + LH \rightarrow L\cdot + L\text{-}OOH$$

After initiation, lipid peroxidation is a self-propagating chain reaction producing lipid hydroperoxides (L-OOH). On the basis of this study, we suggest that 2,6-diisopropylphenol (PH) interferes with lipid peroxidation via a process of hydrogen abstraction:

$$L\text{-}OO\cdot + PH \rightarrow P\cdot + L\text{-}OOH$$

The phenoxyl radical species which is thereby generated (P·, the phenoxyl radical which we have identified in these ESR experiments) is not reactive enough to propagate lipid peroxidation itself as a result of the free electron of this species being distributed throughout the phenol ring of the compound, and lipid peroxidation is therefore arrested. The TRAP assay experiments demonstrate that each molecule of propofol scavenges two radicals, suggesting that 2,6-diisopropylphenol behaves in a manner similar to vitamin E [11], with P· reacting with a further lipid peroxyl radical to form a stable non-radical adduct.

The clinical significance of these observations is not clear. Theoretically, the maximum contribution to plasma antioxidant potential made by propofol is $2x$, where x is the concentration of propofol (µmol litre^{-1}). At a concentration of 20 µg ml^{-1}, equivalent to 112 µmol litre^{-1}, we observed an increase in plasma TRAP of 215 µmol litre^{-1}, which is close to the predicted value of 224 µmol litre^{-1}. (As the plasma protein binding of propofol is quoted as 97–98% [12], it would appear that, in this system at least, total plasma propofol, rather than just free propofol, is available as an antioxidant.) However, as the anaesthetic concentration of propofol is in the range 2–5 μg ml^{-1} (11–28 μmol $litre^{-1}$) [13], the expected increase in plasma TRAP during propofol anaesthesia would only be in the region of 20–60 μmol $litre^{-1}$, which would not be a significant contribution, given that the normal range of fasting plasma TRAP values is 600–1000 μmol $litre^{-1}$. Nevertheless, as the major lipid-soluble plasma antioxidant is vitamin E, and this comprises only 5–10 % of plasma TRAP (that is, 50–100 μmol $litre^{-1}$) [6], this would represent a doubling of the lipophilic component of the antioxidant capacity of plasma.

Whilst the effect of propofol on plasma antioxidant activity appears to be modest, the similarities between 2,6-diisopropylphenol and vitamin E suggest that attention might be better directed towards its possible effect on tissue antioxidant defences. Vitamin E, present in only small quantities in plasma, plays a crucial role in protecting the lipophilic environment of the cell membrane against oxidant stress [1, 14]. *In vitro*, vitamin E protects endothelial cells [15] and erythrocyte suspensions [11] against free radical-mediated injury. *In vivo*, its deficiency is associated with a variety of acute and chronic conditions [16], although its therapeutic value in the absence of established deficiency is unproven, particularly in the acute situation. This may be a consequence, however, of the prolonged time required for administered vitamin E to increase tissue concentrations [17]. In contrast, propofol accumulates in biomembranes far more readily, so that it may be able to boost the antioxidant defences of tissues and, more specifically, lipophilic membrane environments far more rapidly. Considerable further investigation is required before such a hypothesis can be established.

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British Journal of Anaesthesia 1992; **68**: 619–620

SHORT COMMUNICATIONS

BRADYCARDIA AND VECURONIUM: COMPARISON WITH ALCURONIUM DURING CHOLECYSTECTOMY

C. P. J. MORTON AND G. B. DRUMMOND

SUMMARY

We have compared the incidence of bradycardia in two groups of patients undergoing cholecystectomy. Twenty consecutive patients were allocated randomly to receive either vecuronium (n = 8) or alcuronium (n = 12) as part of a standard anaesthetic technique. Bradycardia was defined as a heart rate less then 50 beat min^{-1}. Five episodes of bradycardia occurred with vecuronium and none with alcuronium (P < 0.01).

KEY WORDS

Neuromuscular relaxants: vecuronium. Complications: bradycardia.

When first introduced into anaesthetic practice, vecuronium was considered to be devoid of cardiovascular side effects. Subsequently, several reports have been published of bradyarrhythmias associated with its use, often in association with other drugs or surgical procedures known to cause slowing of the heart. One study [1] concluded that vecuronium has no intrinsic bradycardic activity; therefore, it may be that bradycardia associated with vecuronium occurs either in the presence of other drugs that can slow the heart or during operations that induce vagal reflexes. The first of these hypotheses has been confirmed [2], but no previous study has compared vecuronium with another agent in a homogeneous group of patients to test the second. This study was designed to compare the incidence of bradycardia during cholecystectomy, which may cause cardiac slowing [3], in patients allocated randomly to receive either vecuronium or alcuronium for neuromuscular block.

METHODS AND RESULTS

After Ethics Committee approval and informed consent, we studied 20 patients (ASA I–II) undergoing elective cholecystectomy. Patients received oral temazepam 20 mg for premedication. Anaesthesia was induced with thiopentone 3–5 mg kg^{-1}, tracheal intubation was facilitated with suxamethonium 100 mg and anaesthesia maintained with oxygen, nitrous oxide and enflurane. According to a previously established randomization table, patients then received either vecuronium (group V, $n = 8$) or alcuronium (group A, $n = 12$) in increments at 4-min intervals until one twitch of the train-of-four remained. Thereafter, neuromuscular block was monitored continuously and maintained at this level. During surgery, the ECG trace was displayed continuously and the low alarm set at 50 beat min^{-1}, bradycardia being defined as a heart rate less than this. All episodes of bradycardia were recorded. Morphine was given i.v. in increments of 2–3 mg as clinically indicated. Depth of anaesthesia was judged clinically using systolic arterial pressure and other clinical signs and maintained constant by altering the inhaled enflurane concentration.

The incidence of bradycardia in the two groups was compared using Fisher's exact test.

The characteristics of each group and the results are shown in table I. In general, group V were older, shorter and weighed less that group A. This may be because seven of the eight patients in group V were male. Five of eight patients in group V developed bradycardias, whereas none occurred in group A ($P < 0.01$). All bradycardias occurred during manipulation of the gall bladder. Four patients were given atropine i.v. in increments (0.3–0.6 mg total dose).

COMMENT

Our study confirms that when vecuronium is used in patients undergoing surgery that can induce reflex vagal efferent action, bradycardia is common. Although physique and sex distribution differed between our two groups, both neuromuscular blocking drugs were titrated to the same neuromuscular block and the differences in body size are unlikely to have influenced the results. The dose of morphine used was small and similar in both groups. At the

TABLE I. *Characteristics of patient groups and results (numbers or median ((range or interquartile range)).* **P < *0.01*

	Group A	Group V
n	12	8
Male	5	7
Age (yr)	54 (24–72)	65 (32–86)
Ht (cm)	168 (159, 172)	158 (156, 162)
Wt (kg)	77 (58, 88)	62 (48, 83)
Body weight > 10% expected	5	3
Bradycardia	0	5**

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time of bradycardia, no patient had received more than 4 mg of morphine and this dose is unlikely to have influenced heart rate [4].

The relationship between vecuronium and bradycardia has been investigated elsewhere. Cozanitis, Pouttu and Rosenberg [5] compared bradycardias associated with vecuronium and pancuronium and found the incidence was greater with vecuronium. However, their patients were undergoing a variety of different operations with potentially different degrees of vagal stimulation and were also given varying doses of fentanyl—a drug which increases vagal efferent activity. In addition, pancuronium is markedly vagolytic.

In the absence of surgical stimulus or vagotonic drugs, vecuronium does not alter heart rate in anaesthetized patients [1] and therefore the bradycardia is likely to be a result of the combination of vecuronium with either surgical procedures that can induce reflex vagal efferent action or other drugs that can slow the heart. Our study confirms the first of these hypotheses. The second has been confirmed by Salmenpara and colleagues [2], who studied patients anaesthetized with fentanyl 75 $\mu g\ kg^{-1}$ before the start of surgery. Vecuronium 0.1 $mg\ kg^{-1}$ caused a significant decrease in heart rate.

Bradycardia could occur because vecuronium either fails to mask, or amplifies, the efferent pathway of the vagal reflex. The exaggeration of the bradycardia caused by fentanyl suggests that the mechanism is one of amplification. The site of action could be either the conducting system of the heart itself or at the ganglia of its autonomic innervation. Bellis, Day and Barnes [6] reported that *in vitro* vecuronium did not sensitize the heart to the chronotropic effects of acetylcholine. This suggests that vecuronium produces its bradycardia by acting on the autonomic ganglia. Prevention of reflex bradycardia of this nature could be achieved most simply by antimuscarinic agents such as atropine or glycopyrronium, but alternative neuromuscular blocking agents that do not possess the properties of vecuronium may also be useful [5].

In conclusion, when used in patients undergoing surgery involving reflex vagal efferent action, vecuronium is associated with a high incidence of bradycardia. Previous work suggests that this effect may be mediated by amplifying efferent vagal activity by action on autonomic ganglia.

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EFFECT OF PETHIDINE PREMEDICATION AND HALOTHANE ANAESTHESIA ON UPPER LIMB BLOOD FLOW

A. L. PAUCA

SUMMARY

Forearm blood flow (FBF), hand blood flow (HBF) and arterial pressure were measured in 12 patients, before and after premedication with pethidine and during halothane anaesthesia. After pethidine there was a significant ($P < 0.01$) increase in HBF (180%) and decreased hand vascular resistance; heart rate also increased significantly ($P < 0.05$), whilst mean arterial pressure (MAP) did not change. The large increase in HBF without hypotension suggests a local effect. With halothane, there was a significant ($P < 0.05$) decrease in MAP, increase in HBF and decrease in hand vascular resistance compared with either control or effects produced by pethidine; there was a significant decrease in FBF and reversal of the action of pethidine on forearm vascular resistance.

KEY WORDS

Anaesthetics, volatile: halothane. Blood: flow, forearm. Premedication: pethidine.

Pethidine and morphine have similar analgesic effects, but pethidine causes cardiovascular depression [1] and suppresses postanaesthetic shivering [2]. Effects attributable to vasodilatation have been studied extensively in the case of morphine [3], but information on effects of pethidine is scant [4]. In addition, it is not known if pethidine pretreatment modifies the well known effects of halothane anaesthesia, including marked increases in hand blood flow (HBF) and moderate decreases in muscle blood flow [5]. This study has examined simultaneously the effects on HBF and forearm blood flow (FBF) of pethidine premedication, and then those of halothane inhalation.

METHODS AND RESULTS

After Institutional Ethics Committee approval, we studied, before surgery, in a room at 24±1 °C, 12 men requiring general anaesthesia for urological procedures who consented to participate. They were aged 30–59 yr, weighed 58–71 kg, had normal body habitus and no cardiorespiratory pathology. In one patient equipment failure prevented the study of the effects of halothane. Anaesthesia was induced with 0.5–1.5% halothane in oxygen and held at this for 5–8 min while blood flows were recorded. Spontaneous ventilation was maintained.

FBF was measured in one arm by mercury-in-rubber strain-gauge and HBF in the other by water plethysmography [5]. Flows were recorded for 2 min and averaged, before premedication, 60 min after pethidine 100 mg and during steady-state halothane anaesthesia.

Arterial pressure was measured by sphygmomanometry and mean arterial pressure (MAP) calculated by adding 33% of the pulse pressure to the diastolic pressure. Forearm and hand vascular resistance were obtained by dividing MAP by FBF and HBF, respectively. Heart rate was obtained from the plethysmographic pulsations. Pa_{CO_2} and Pa_{O_2} were measured during steady-state halothane anaesthesia.

Overall drug effect was evaluated by univariate repeated measures analysis of variance, with $P < 0.05$ considered significant. Correlations were sought among the appropriate changes in the variables measured. All results are expressed as mean (SEM).

The effects of pethidine included: a significant increase in heart rate from 64 (SEM 2) to 75 (4) beat min^{-1}; a significant increase in HBF from 7.0 (1.2) to 19.7 (1.9) ml/dl of tissue min^{-1} and concomitant decrease in hand vascular resistance from 19.4 (3.5) to 5.9 (0.6) arbitrary units (MAP/HBF); an increase in FBF, from 5.2 (0.6) to 7.0 (0.5) $ml/dl^{-1}\ min^{-1}$ ($P = 0.058$); and a significant decrease in forearm vascular resistance from 23.5 (2.7) to 15.8 (1.5) arbitrary units (MAP/FBF).

Halothane significantly increased HBF from 7.0 (1.2) $ml\ dl^{-1}\ min^{-1}$ before (bP), and 19.7 (1.9) $ml\ dl^{-1}\ min^{-1}$ after pethidine (aP), to 34.7 (2.6) $ml\ dl^{-1}\ min^{-1}$; significantly decreased MAP from 104.02 (1.0) mm Hg bP and 103.4 (3.0) mm Hg aP to 89.8 (2.9) mm Hg. It reduced FBF from 5.2 (0.6) $ml\ dl^{-1}\ min^{-1}$ bP ($P = 0.058$) and 7.0 (0.5) $ml\ dl^{-1}\ min^{-1}$ aP ($P < 0.05$) to 4.9 (0.6) ml $dl^{-1}\ min^{-1}$. It significantly increased forearm vascular resistance from 15.8 (1.5) arbitrary units bP to 21.5 (2.7) arbitrary units. Blood flow changes did not correlate with those in arterial pressure, heart rate or ventilatory frequency. During halothane anaesthesia, Pa_{O_2} exceeded 13 kPa and Pa_{CO_2} was 6.8 (0.1) kPa.

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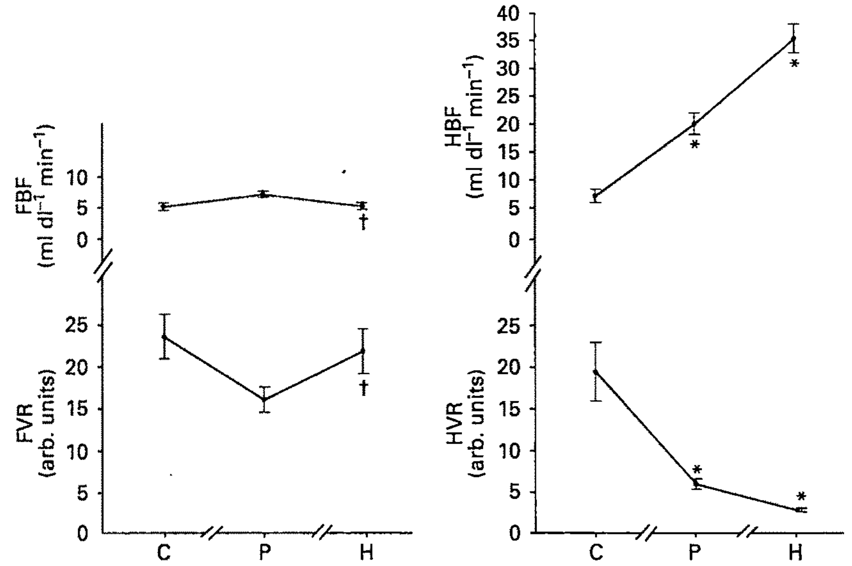

FIG. 1. Effect of pethidine (P) and addition of halothane (H) on forearm (FBF) and hand (HBF) blood flows and vascular resistances (FVR, HVR). arb. units = Arbitrary units. C = Control. $P < 0.05$ compared with: *control; †pethidine.

COMMENT

A large increase in skin or muscle FBF causes systemic hypotension. The moderate increase in FBF (35 %) produced by pethidine, which agrees with previous reports [4], reflects the relative stability of these patients; usually they become symptomatic only in response to tilting or rapid, inert body movement. In contrast, the hand vasoregulatory mechanism is not shared with other major body areas [5]; this is illustrated by the large increase in HBF (181 %) produced by pethidine, in the presence of unchanged MAP. A generalized increase of this magnitude would require a similar increase in cardiac output, which pethidine does not produce [1].

The increase in HBF that halothane produced over that caused after pethidine premedication (fig. 1) suggests the possibility that pethidine increased HBF by its sedative effect, which partially inhibits the normal sympathetic vasoconstriction present in the hand, similar to the effects of thiopentone and nitrous oxide [5], while halothane seems to add a selective local inhibition of the action of catecholamines on skin vessels [6]. The effect of halothane on FBF is compounded by the increase in blood flow produced by pethidine. If this increase is in skin, via release of histamine, it is possible that halothane would not modify this state and its effect on FBF would seem diminished. Although we avoided controlled ventilation and distress, which alter forearm muscle blood flow, it is possible that mild hypercapnia developed, which increases FBF in muscle [5]. Because halothane reduces muscle blood flow via liberation of vasopressin [6], even in the presence of hypercapnia [5], it may be assumed that the reduction in FBF during the interval between pethidine and halothane administration occurred in muscle.

In summary, premedication with pethidine produced a large increase in HBF, restricted to the skin of the hand, and a smaller increase in FBF. The increase in FBF was confined to muscle, as it was suppressed by halothane. The addition of halothane further increased HBF and neutralized the forearm vasodilator effect of pethidine.

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CASE REPORT

SEVERE HYPERTENSION DURING POSTPARTUM HAEMORRHAGE AFTER I.V. ADMINISTRATION OF PROSTAGLANDIN E_2

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SUMMARY

Severe hypertension with arterial spasm was observed after i.v. administration of prostaglandin E_2 (PGE_2) during uterine exploration under general anaesthesia for control of postpartum haemorrhage. This hypertension was exceptional because PGE_2 is known to cause a decrease in systemic arterial pressure. Different hypotheses for this paradoxical hypertensive crisis after PGE_2 administration are discussed.

KEY WORDS

Anaesthesia: obstetric. Complications: hypertension, postpartum haemorrhage. Hormones: prostaglandin E_2.

Prostaglandin E_2 (PGE_2) has been used in obstetrics as a mid-trimester abortifacient and in treatment of uterine atony. It is known to cause several clinical signs such as pyrexia, increase in heart rate and tachypnoea, but the main problem of concern to the anaesthetist is hypotension [1, 2]. In the patient described here, we observed severe hypertension and peripheral arterial spasm after administration of PGE_2.

CASE REPORT

A 38-yr-old woman was admitted to hospital for Caesarean section because of a scarred uterus. She had a history of childhood asthma and a previous Caesarean section 2 yr earlier under general anaesthesia for feto–maternal disproportion.

As the preoperative evaluation of the patient was normal (ASA I), Caesarean section was planned electively to take place at 11:00 under general anaesthesia. After preoxygenation of the lungs, anaesthesia was induced using a rapid sequence technique with cricoid pressure and thiopentone 250 mg followed by suxamethonium 80 mg i.v. A 7.5-mm oral tracheal tube was inserted under direct vision. Anaesthesia was maintained with 65% nitrous oxide in oxygen and neuromuscular block was produced with vecuronium 8 mg. The patient received fentanyl 100 µg and 0.75% isoflurane after delivery of the baby. During surgery, arterial pressure and heart rate remained stable at about 120/75 mm Hg and 75 beat min^{-1}, respectively. At the end of surgery, the surgeon noted that the uterus was not contracted, although the patient had received oxytocin 5 u i.v., followed by an i.v. infusion of another 15 u after delivery. In an attempt to stimulate uterine contraction, the obstetrician injected oxytocin 20 u directly into the myometrium before closing the abdominal wall, without apparent effect. The surgical procedure lasted until 11:55, after which the patient was admitted to the recovery room. The baby was in good condition, with an Apgar score of 9 at 10 min.

Because of postpartum haemorrhage caused by uterine atony that had failed to respond to i.v. oxytocin, neuromuscular block was not antagonized, intubation of the trachea was maintained and the patient was kept sedated with repeated i.v. administration of midazolam. After estimated total blood loss exceeded 2 litre, it was decided to explore the uterus under general anaesthesia, and at 14:00 the patient was readmitted into the operating room.

At this time she had received colloidal solution 2 litre, her arterial pressure was 100/70 mm Hg and heart rate 90 beat min^{-1}. Haematological investigation showed that her haemoglobin concentration was 6.6 g dl^{-1} (compared with 11.8 g dl^{-1} before surgery) and a transfusion of packed red blood cells 6 u was started. Anaesthesia was induced and maintained with fentanyl, midazolam, vecuronium and 50% nitrous oxide in oxygen. After uterine exploration, because of continuing haemorrhage after oxytocin and uterine massage, at 14:30 the obstetrician injected blindly through the abdominal wall, directly into the myometrium, 0.5 mg of PGE_2 diluted in 0.9% saline 5 ml. Concomitantly an infusion of 500 ml of fluid containing PGE_2 1 mg was commenced in order to stimulate uterine contraction. A few minutes later, we observed severe hypertension: 220/120 mm Hg measured twice by automated device (Dinamap). At the same time, we noted that the peripheral pulses of the two arms were no longer palpable whilst, in contrast, the carotid arteries were easily palpable. The skin was colourless

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and it was difficult to measure arterial pressure by auscultation. We attributed this situation to severe peripheral arterial spasm, confirmed by attempts to cannulate the left radial artery. We decreased the rate of infusion of PGE$_2$ and, a few minutes later, arterial pressure was normal (125/80 mm Hg) and we finally succeeded in inserting an arterial cannula for monitoring arterial pressure. Thirty minutes later there was little further bleeding from the uterus, which was well contracted. The patient was returned to the recovery room and the trachea was extubated when spontaneous ventilation had returned and the patient was awake. Coagulation screen and full blood count after operation were normal. A few days later, echocardiography was also normal and the patient eventually made a good recovery.

DISCUSSION

In this case report, we described severe hypertension and clinical signs suggestive of peripheral arterial spasm after i.v. administration of PGE$_2$. This hypertension cannot be attributed to any mistake in administration of drugs, and there was no evident interaction between PGE$_2$ and anaesthetic drugs. Our patient had never been treated with hypertensive drugs or been diagnosed as having essential hypertension.

We have found two cases of severe hypertension after administration of PGF$_{2\alpha}$ during anaesthesia in the literature [3, 4]; in each case the cause was unexplained.

Prostaglandins are used commonly in obstetrics for stimulant actions on uterine muscle [5]. In our patient, this action of PGE$_2$ allowed control of postpartum atony. Usually, PGE$_2$ causes vasodilatation and a reduction in systemic vascular resistance [1].

Central pressor effects of prostaglandins (hypertension and tachycardia) have been observed in dogs after direct injection into the brain or into the carotid artery. These effects may have been mediated either by an increase in central cholinergic activity or by an increase in catecholamine release from the anterior hypothalamus [6]. Because prostaglandins are metabolized rapidly in the lungs, the plasma concentration of prostaglandin reaching the brain is probably insufficient to elicit these centrally mediated effects after i.v. administration, but adequate to

[redacted]

lung was inadequate to prevent central stimulation caused by increased arterial circulation.

Second, patent foramen ovale (PFO). A PFO exists in approximately 25% of the population [7]. Transitory opening of a PFO could have occurred through an increase in right atrial pressure which may occur during controlled ventilation [8], leading to large arterial concentrations of PGE$_2$ and central stimulation. Contrast echocardiography was performed in our patient, but this was negative [9]; nonetheless, the PFO may have been opened only when the patient was subject to controlled ventilation.

Third, release of renin by the uterus, kidney or both. It has been shown in the dog that a continuous infusion of PGE$_2$ into the renal artery causes an increase in systemic arterial pressure by activation of the renin–angiotensin system [10, 11].

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APPARATUS

PHYSICAL CHARACTERISTICS OF AN ENCLOSED AFFERENT RESERVOIR BREATHING SYSTEM

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SUMMARY

We have assessed the characteristics of the Ohmeda Enclosed Afferent Reservoir Breathing System (EAR) using simulated spontaneous ventilation and controlled ventilation. The additional work of breathing through the system was measured and shown to be comparable to that of a modified Mapleson D breathing system (Bain) for fresh gas flows producing similar end-tidal carbon dioxide concentrations. It was shown under conditions of simulated controlled ventilation that end-tidal gas concentration was relatively insensitive to variations in inspired to expired ratio (I:E), tidal volume ($\dot{V}$T) and deadspace ($\dot{V}$D). Measurement of the volume of carbon dioxide rebreathed using simulated spontaneous ventilation led to the prediction that rebreathing of carbon dioxide would begin to occur in the EAR when fresh gas flow to total ventilation ratio ($\dot{V}$F:$\dot{V}$E) was approximately 0.87. However, comparison of the results of model lung tests and clinical data suggests that great caution should be taken in extrapolating such results into clinical advice.

KEY WORDS

Equipment: breathing systems, EAR system.

An enclosed afferent reservoir (EAR) breathing system is essentially a modified Mapleson A system with an enclosed reservoir and a distal expiratory valve. It has been suggested that such systems approach the ideal breathing system, having the advantages of high efficiency of fresh gas usage during both spontaneous ventilation and controlled ventilation [1–6]. We report here the results of laboratory testing of the Ohmeda EAR, the clinical trials of which have been reported elsewhere [7–9]. The tests were performed during simulated and controlled ventilation to measure the effect of changes in deadspace, tidal volume and inspired to expired (I:E) ratio on end-tidal carbon dioxide concentration. The values of the fresh gas flow to total ventilation ($\dot{V}$F:$\dot{V}$E) ratio when rebreathing of carbon dioxide occurred and the additional work of breathing imposed by the system were determined during simulated spontaneous ventilation.

THE OHMEDA EAR BREATHING SYSTEM

A schematic diagram of the Ohmeda EAR Breathing System is shown in figure 1. The enclosed reservoir is a rising bellows inside a transparent bellows housing. Fresh gas flow passes directly into this bellows and a second port from the base of the bellows is connected to the inspiratory limb of the system. From the patient Y-piece at the right hand side of the figure, an expiratory limb returns to an expiratory valve vented to atmosphere or a gas scavenging system. This expiratory valve is pressure-controlled by a balloon connected to the space between the bellow housing and the bellows. The breathing system is integrated for controlled ventilation with an Ohmeda 7800 ventilator which drives the bellows as a "bag in a bottle". This ventilator monitors inspiratory flow using the anemometer flow transducer at the patient Y-piece and is controlled electronically using the integrated anemometer signal. It is a mixed cycle ventilator for which the user may set I:E ratio, total ventilation and tidal volume.

A self-inflating bag enables the patient's lungs to be ventilated manually either during spontaneous ventilation or at any time during controlled ventilation.

The action of the breathing system during inspiration differs between controlled ventilation and spontaneous ventilation. During controlled ventilation, the ventilator creates a pressure increase in the space between the bellows and the bellows housing. The expiratory valve is closed by the balloon sealing the expiratory limb and the bellows descends. Gas is thus forced into the patient's lungs. In spontaneous ventilation, the bellows descends because of the sub-atmospheric pressure generated at the patient's mouth. The expiratory valve closes under its own weight.

During expiration, the action of the system is the same during both spontaneous ventilation and

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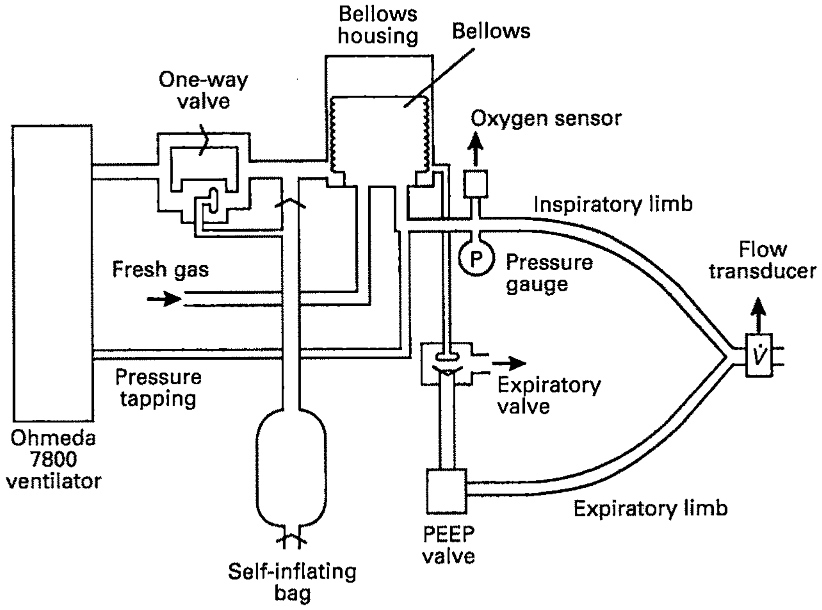

FIG. 1. Schematic diagram of the Ohmeda EAR.

controlled ventilation. During the early part of expiration, expired gas and fresh gas fill the bellows and the expiratory valve remains closed under its own weight. Expired gas flows into the inspiratory limb until the bellows reaches the top of the bellows housing. Before this, the pressure in the system is less than the 1.9 cm H_2O required to open the expiratory valve. However, as soon as the bellows reaches the top of the housing, the expiratory valve pressure is exceeded and the expiratory valve opens. Fresh gas now flows through the bellows and into the inspiratory limb, the bellows remaining at the top of the housing. Expiratory gas escapes through the expiratory limb after the opening of the expiratory valve. As in the Mapleson A (Magill) system, fresh gas flowing into the inspiratory limb tends to clear the inspiratory limb of expired gas towards the end of expiration, provided there is sufficient fresh gas flow to fill the bellows and open the expiratory valve.

REBREATHING STUDIES

Controlled ventilation

Although the amount of rebreathed carbon dioxide in controlled ventilation is of little interest clinically, it is of interest to designers of breathing systems. Thus, for completeness, the amount of carbon dioxide rebreathed in controlled ventilation was measured.

The system was connected to a model lung constructed from a clear plastic box containing an impermeable plastic bag. Carbon dioxide was injected into this bag via a multi-branched pipe, which had the effect of supplying gas to all parts of the bag, thereby producing "physiological gas mixing" and a realistic output capnograph. The outer part of the box was connected to a Manley test lung to provide elastic recoil. Gas from the Y-piece was sampled at a rate of 20 ml min^{-1} and carbon dioxide was measured using a Ohmeda MGM 2000 mass spectrometer. Simulation of a 70-kg subject was performed using carbon dioxide 180 ml min^{-1} delivered from a calibrated rotameter (Gap meter).

Four experiments were performed:

(1) The effect of varying $\dot{V}$F between an equivalent of 30–240 ml kg^{-1} min^{-1} was measured with total ventilation ($\dot{V}$E) fixed at an equivalent of 100 ml kg^{-1} min^{-1}.

(2) The effect of varying $\dot{V}$E between an equivalent 20 and 200 ml kg^{-1} min^{-1} with $\dot{V}$F fixed at 100 ml kg^{-1} min^{-1} was measured.

(3) End-tidal carbon dioxide concentration was plotted for various ratios of deadspace to tidal volume with a $\dot{V}$F : $\dot{V}$E ratio of 1 and an I:E ratio of 1:2. Deadspace was varied by introducing lengths of tubing between the breathing system and the model lung. The volumes of these tubes were estimated volumetrically.

(4) The ventilator was set to give a tidal volume of 700 ml and used to generate a range of values of I:E between 2.5:1 and 1:4 with $\dot{V}$F : $\dot{V}$E fixed at 1.

Spontaneous ventilation

To determine the onset of rebreathing for the EAR during spontaneous ventilation, the model lung was connected to a sinusoidal flow generator and used to simulate spontaneous ventilation. The supply of carbon dioxide was maintained at 180 ml min^{-1} with a ventilatory frequency of 12 b.p.m. at a tidal volume of 500 ml.

Four clinical methods of defining rebreathing were tested using this apparatus in a manner similar to that reported by Chan, Bruce and Soni [4]. Fresh gas flow was reduced until end-tidal or end-inspiratory carbon dioxide concentration was seen to increase by a known amount. The rebreathing points used in clinical studies by Kain and Nunn [10], Norman, Adams and Sykes [11], Humphrey [12] and Dixon, Chakrabarti and Morgan [13] were then applied to the results. Whilst the clinical methods of defining rebreathing were being tested, a microcomputer system and a computer program were used to calculate the volume of carbon dioxide inspired per breath as fresh gas flow was reduced.

RESISTANCE TO BREATHING

Resistance of the EAR to breathing was determined dynamically by measuring the additional work of breathing as described by Kay and colleagues [14]. The system was connected directly to a sinusoidal flow generator which was set to deliver tidal volumes of 500 ml at a breathing frequency of 12 b.p.m. A pneumotachograph and pressure transducer were attached between the output of the flow generator and the breathing system. The apparatus was calibrated using a water manometer and a known tidal volume obtained from the flow generator calibrated previously against a spirometer. Additional work of breathing per breath during the inspiratory and expiratory periods was measured. A range of other breathing systems were tested concurrently on the same system to facilitate comparison.

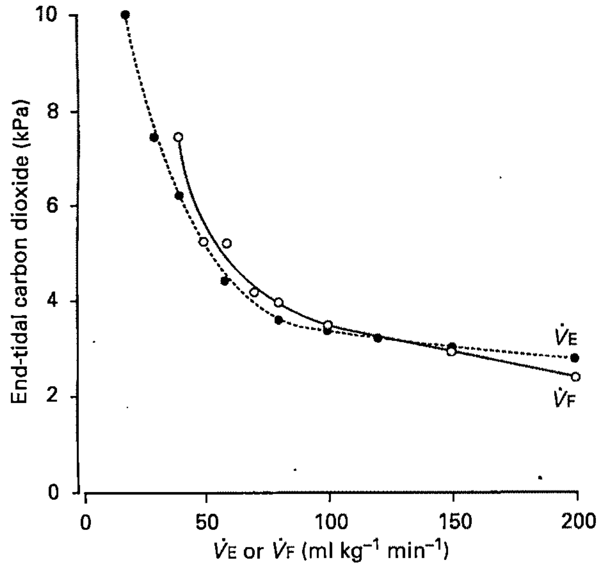

FIG. 2. Simulated controlled ventilation: end-tidal partial pressure of carbon dioxide *vs* variation in total ventilation ($\dot{V}$E) (●) and in fresh gas flow ($\dot{V}$F) (○). I:E = 1:2; fixed $\dot{V}$E or $\dot{V}$F = 100 ml kg^{-1} min^{-1}.

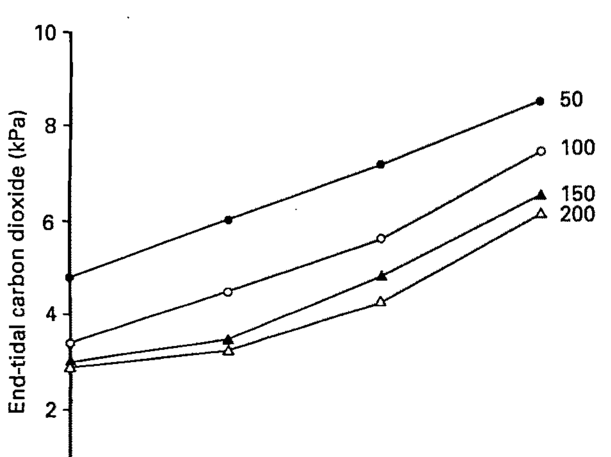

FIG. 3. Simulated controlled ventilation: change in end-tidal partial pressure of carbon dioxide with changes in anatomical deadspace to tidal volume ratio (VD/VT) for various values of $\dot{V}$E: 50 (●), 100 (○), 150 (▲) and 200 (□) ml kg^{-1} min^{-1}.

RESULTS

Rebreathing—controlled ventilation

The effects on end-tidal partial pressure of carbon dioxide of varying $\dot{V}$F whilst holding $\dot{V}$E constant, and of varying $\dot{V}$E whilst holding $\dot{V}$F constant, were tested. $\dot{V}$E and $\dot{V}$F were each held equivalent to 100 ml kg^{-1} min^{-1}. The results (fig. 2) showed general characteristics similar to those for other breathing systems demonstrated by Stockwell, Bruce and Soni [15].

The effect on end-tidal carbon dioxide of change in deadspace to tidal volume ratio is shown in figure 3.

The effect of changes in I:E ratio on end-tidal partial pressure of carbon dioxide is shown in figure 4.

Rebreathing—spontaneous ventilation

Figure 5 shows the effect on end-tidal and end-inspired partial pressures of carbon dioxide with

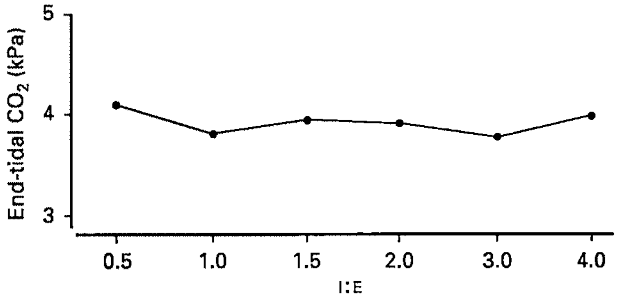

FIG. 4. Simulated controlled ventilation: variation of end-tidal partial pressure of carbon dioxide with I:E ratio ($\dot{V}$F: $\dot{V}$E = 1).

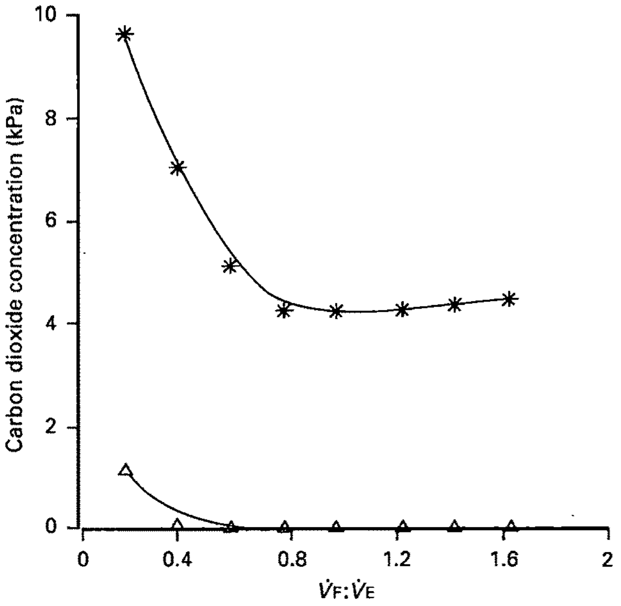

FIG. 5. Simulated spontaneous ventilation: variation in end-tidal (*) and inspired (△) partial pressures of carbon dioxide with $\dot{V}$F: $\dot{V}$E ratio (I:E = 1:2).

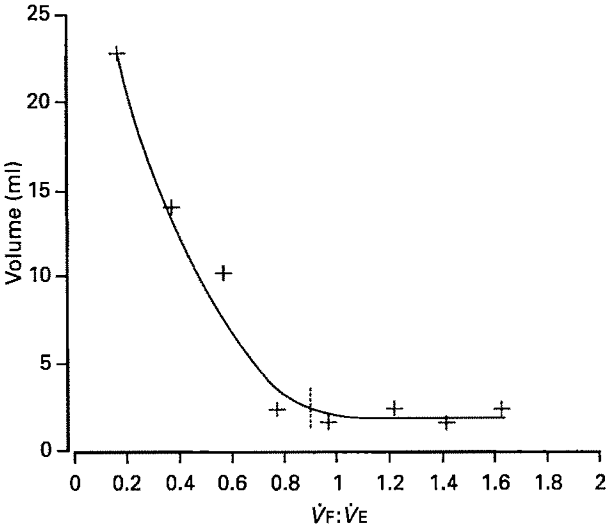

FIG. 6. Simulated spontaneous ventilation: volume of carbon dioxide rebreathed for various I:E ratios *vs* $\dot{V}$F:$\dot{V}$E ratio (I:E = 1:2).

changes in $\dot{V}$F:$\dot{V}$E ratio. The volume of carbon dioxide rebreathed for changes in $\dot{V}$F:$\dot{V}$E ratio is shown in figure 6.

Additional work of breathing

A comparison of additional patient expiratory work, additional system inspiratory work and total additional work of breathing for three fresh gas flows is shown in table I. Table II shows total work of breathing for three other breathing systems measured concurrently: a Mapleson A (S.M.S. Hiedbrink valve with MIE bag and tubing), an Ohmeda Mk5a Circle and a Mapleson D (S.M.S. Heidbrink valve with MIE bag and tubing).

DISCUSSION

Effect of I:E ratio and increased deadspace

During controlled ventilation, the breathing system is relatively insensitive to a variation in inspiratory to expiratory ratio or to variations in deadspace. Comparison of simulated results with those reported by Stockwell, Bruce and Soni [15], who examined the influence of physiological deadspace on end-tidal carbon dioxide tension using a controlled ventilation lung model, shows that the EAR breathing system compares favourably with both a Bain and the Humphrey A.D.E. The system is more stable to changes in I:E ratio than was the T-piece tested by Rose and Froese [16].

TABLE II. *Total additional work of breathing (mean (SEM)) (n = 5) for various breathing systems. Tidal volumes 500 ml, ventilatory frequencies 12 b.p.m.*

Fresh gas flow (litre min^{-1})	Additional total work of breathing (mJ b^{-1})
Mapleson A (Magill)	
6	71 (0.34)
8	81 (5.25)
Circle (Ohmeda Mk5a)	
1	140 (0.30)
4	163 (0.22)
6	226 (1.94)
Mapleson D (Bain)	
6	68 (0.66)
8	89 (0.58)

Defining the point of the onset of rebreathing of carbon dioxide

Several different definitions for the onset of rebreathing have been used in clinical studies. It was defined by Kain and Nunn [10] as a 0.65-kPa increase in end-tidal partial pressure of carbon dioxide; by Norman, Adams and Sykes [11] as an increase of 0.25 kPa in end-tidal carbon dioxide; by Humphrey [12] as a 0.25-kPa increase in inspired partial pressure of carbon dioxide; and by Dixon, Chakrabarti and Morgan [13] as a 0.2-kPa increase in inspired carbon dioxide. Chan, Bruce and Soni [4] applied these criteria to simulated studies on a model lung.

Following the same methodology, predictions for the point of onset of rebreathing from these criteria were made using interpolation using a cubic spline which fits sections of a cubic polynomial curve to the individual sets of data obtained. Onset of rebreathing is predicted at a mean $\dot{V}$F:$\dot{V}$E of 0.68 for the Kain and Nunn criteria, 0.81 for the Norman, Adams and Sykes criteria, 0.33 for Humphrey's criterion and 0.34 for Dixon, Chakrabarti and Morgan criteria.

The results from the laboratory test reported here predict much greater values of $\dot{V}$F:$\dot{V}$E than the application of the same criteria in clinical circumstances. For the Mapleson A (Magill) system, Kain and Nunn [10] found that a mean $\dot{V}$F:$\dot{V}$E ratio of 0.44 in the physiological state marked the onset of rebreathing and Norman, Adams and Sykes [11] showed a mean of 0.55. The discrepancies between the laboratory testing and these clinical results arise because, in patients, changes in end-tidal carbon dioxide tension may be compensated for by changes in breathing pattern, which the model lung is unable to achieve. This change in end-tidal concentration

TABLE I. *Additional work of breathing (mean (SEM)) (n = 5) for the EAR for tidal volumes of 500 ml and ventilatory frequency of 12 b.p.m. (patient inspiratory and system expiratory work were zero)*

Fresh gas flow (litre min^{-1})	Patient work during expiration (mJ b^{-1})	System work during inspiration (mJ b^{-1})	Total work of breathing (mJ b^{-1})
4	85 (0.43)	37 (0.26)	122 (0.50)
6	103 (0.71)	44 (0.91)	147 (1.15)
8	119 (2.45)	50 (0.43)	169 (2.49)

occurs much sooner as fresh gas flow is reduced—that is, at greater $\dot{V}_F:\dot{V}_E$ ratios.

An absolute definition of the onset of rebreathing may be made by measuring the volume of carbon dioxide rebreathed at each breath. The onset of rebreathing would then occur when the volume of rebreathed carbon dioxide increased to greater than zero or some minimum value irreducible by increased fresh gas flow.

It may be seen from figure 6 that, for this definition of rebreathing, the volume of carbon dioxide rebreathed increased significantly from the mean minimum value at $\dot{V}_F:\dot{V}_E$ 0.87.

Monitoring of end-tidal concentration changes with changes in $\dot{V}_F:\dot{V}_E$ and measurements of the absolute volume of rebreathed carbon dioxide show much the same turning points. These turning points are in close agreement with the results of our recent study on children [9] and with the results of Miller [3, 17] which predicted rebreathing for an EAR at $\dot{V}_F:\dot{V}_E$ 0.78.

It is clear that great caution must be exercised in extrapolating the results of laboratory measurements on model lungs to patients.

Effect of the resistance to breathing

The additional work of breathing of the system lies between that of a circle system and that of a Mapleson D (Bain) system (tables I, II). The minimum fresh gas flow required to satisfy the Kain and Nunn criteria for rebreathing carbon dioxide for a Bain system is approximately 1.5 times total ventilation. For a 70-kg man at $\dot{V}_E$ 100 ml kg^{-1} min^{-1}, this gives a fresh gas flow of 10.5 litre min^{-1}. Extrapolating the results shown in table II would give a total additional work of breathing at this flow for the Mapleson D (Bain) of approximately 115 mJ b^{-1}. The equivalent point for the EAR would be at a fresh gas flow of 4.7 litre min^{-1}, giving a total additional work of 130 mJ b^{-1}.

The EAR has a greater total additional work of breathing compared with a Mapleson A (Magill) system. This is not unexpected, as the EAR has a more complex valving system and greater inertia bellows system. Most of the difference occurs in expiration, and may not be particularly significant in a clinical sense. As the fresh gas efficiency of the two systems is similar, the reduction in additional work by operating at lower fresh gas flow has no advantage for the EAR.

ACKNOWLEDGEMENT

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NITROUS OXIDE ADMINISTRATION USING COMMONLY AVAILABLE OXYGEN THERAPY DEVICES

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SUMMARY

Administration of nitrous oxide is useful for providing sedation and analgesia. The therapeutic range for nitrous oxide is 20–30%. Several oxygen treatment devices have been used for administering nitrous oxide, but little is known about the concentrations of nitrous oxide and oxygen delivered to the trachea. We have studied this, using an analogue lung model, with several oxygen therapy devices. With a 1:1 nitrous oxide–oxygen mixture in the primary flow for all systems, end-expired nitrous oxide concentrations varied between 6.5% and 34.3%. Therapeutic concentrations were produced using the Hudson (nominal oxygen concentration 60%) fixed-performance mask, the variable performance Hudson mask at 4 litre min^{-1}, the MC masks at 4 and 6 litre min^{-1} and the nasal prongs at 6 and 8 litre min^{-1}. Simultaneous end-expired oxygen concentrations for all devices tested were within a safe range.

KEY WORDS

Anaesthetics, gases: nitrous oxide. Equipment: oxygen masks. Sedation.

Nitrous oxide is used frequently as an analgesic and sedative agent during operation during regional anaesthesia. It has a history of apparent safety and effective use, but it may depress ventilation [1–3] and circulation [4, 5], particularly in patients with initially compromised function. Parbrook reviewed the concentrations of nitrous oxide required for anaesthesia and analgesia [6]; he concluded that 20–30% nitrous oxide (zones 1–2) provided optimum analgesic and sedative effects.

This study was designed to determine if appropriate concentrations of nitrous oxide and oxygen could be delivered, when oxygen delivery systems were supplied with a 1:1 mixture of nitrous oxide and oxygen. We chose a 1:1 mixture because this is used commonly to supplement regional techniques. Because it is difficult to obtain representative inspired gas concentrations non-invasively in humans, we have used a lung model for spontaneous ventilation.

METHODS

The lung model used [7] produced a sinusoidal ventilatory flow pattern, with a tidal volume of 400 ml, tracheal volume equivalent to the deadspace (130 ml) and minute ventilation of 6 litre min^{-1}. The peak inspiratory flow rate (PIFR) was measured with a Fleisch pneumotachograph and found to be 20 litre min^{-1}. A Laerdal face shield was used to simulate a patient–mask interface.

The lung model is not involved in gas exchange and therefore equilibrates eventually with the mixed-inspired concentration, which in the model is equivalent to the alveolar concentration; the lung model acts as a volume-weighted averager of the inspiratory concentration. In a patient, at the end of expiration the deadspace is filled with end-tidal gas which contains a different concentration of nitrous oxide and forms part of the mixture that enters the alveoli on the next inspiration. However, this effect is small when equilibrium is approached with the inspired nitrous oxide concentration. Therefore, end-expired concentrations of gases were measured as a reflection of the alveolar gas concentration and hence, in the lung model, of the mixed-inspired concentration.

Gas concentrations were measured at the "subglottic" level via a catheter attached to a mass spectrometer (Centronics 200 MGA). The mass spectrometer was calibrated with a British Oxygen Company certified gas mixture; zero for each gas was established using a 100% concentration of another gas. A computer with a multi-channel chart program was used to record the signals from the mass spectrometer. The end-expiratory concentrations of nitrous oxide and oxygen were noted. At each stage of the study, equilibration of gases in the mechanical lung model was permitted for 20 min. Duplicate measurements were performed on each breathing system.

The oxygen delivery devices used included Ventimask and Hudson mask (nominal oxygen concentrations 40% and 60% at gas flows of 10 litre min^{-1} and 15 litre min^{-1}, respectively), Mary Catterall mask (gas flows of 4 litre min^{-1} and 6 litre min^{-1}) and nasal prongs (gas flows of 2, 4, 6 and 8 litre min^{-1}). In addition, the Hudson mask was used as a variable performance device at flow rates of 4 litre min^{-1} and 6 litre min^{-1}.

The 50% nitrous oxide in oxygen driving gases were delivered from a Boyle's anaesthetic machine. The gas flow rates were checked using a rotating

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Table I. *End-expiratory nitrous oxide (E'_{N_2O}) and oxygen (E'_{O_2}) concentrations obtained for the fixed-performance masks. Vf = fresh gas flow. Theoretical values for nitrous oxide based on calculation of the entrainment ratio (see Appendix) are given in parentheses*

Delivery system	$\dot{V}f$ (litre min^{-1})	E'_{N_2O} (%)	E'_{O_2} (%)
Ventimask 40%	10	13.6 (12)	30.8
Hudson 40%	10	6.5 (12)	25.9
Ventimask 60%	15	31.7 (24.7)	42.4
Hudson 60%	15	20.4 (24.7)	35.0

Table II. *End-expiratory nitrous oxide (E'_{N_2O}) and oxygen (E'_{O_2}) concentrations obtained for the variable-performance masks. Vf = fresh gas flow*

Delivery system	$\dot{V}f$ (litre min^{-1})	E'_{N_2O} (%)	E'_{O_2} (%)
Hudson	4	28.0	40.1
MC	4	25.3	37.3
Hudson	6	34.3	44.4
MC	6	28.5	40.4

Table III. *End-expiratory nitrous oxide (E'_{N_2O}) and oxygen (E'_{O_2}) obtained for the nasal prongs. Vf = fresh gas flow*

$\dot{V}f$ (litre min^{-1})	E'_{N_2O} (%)	E'_{O_2} (%)
2	7.8	26.4
4	14.1	29.8
6	20.0	33.4
8	23.1	35.5

bobbin flowmeter (Gap-Meter A_{10} and A_6) calibrated previously against a dry spirometer of known accuracy (Ohio 840). The ratio of nitrous oxide to oxygen delivered was maintained at 1:1. The design performances of the fixed-performance masks were tested also with 100% oxygen, to validate the manufacturer's stated oxygen delivery.

RESULTS

When the fixed-performance Ventimask was supplied with 100% oxygen, the delivered concentrations of oxygen were 40.2% and 62.4% with the 40% and 60% nominal concentration masks, respectively. For the Hudson masks, the corresponding concentrations were 40.4% and 59.7%. Therefore, at a PIFR of 20 litre min^{-1}, these results are in close agreement with the oxygen delivery as stated by the manufacturers.

The mean end-expiratory concentrations of nitrous oxide and oxygen and the gas flows used for each of the three different types of devices tested (fixed-performance masks, variable-performance masks and nasal prongs), are summarized in tables I, II and III. The maximum difference in gas concentrations between duplicate measurements was less than 1%.

DISCUSSION

Previous *in vivo* studies of gas concentrations delivered by oxygen masks supplied with nitrous oxide and oxygen mixtures were affected by variations in inspiratory flow rate, tidal volume and end-expiratory pause, with varying nitrous oxide and oxygen entrainment. Leigh showed that variations were reflected by changes in end-tidal carbon dioxide [8]. The use of the mechanical lung model overcomes some of these problems.

This study has revealed wide variations in the mixtures delivered by different systems: 6.5–34.3% for nitrous oxide and 25.9–44.4% for oxygen. Amongst the fixed-performance masks, only the Hudson 60% gave a nitrous oxide concentration within the 20–30% range, although the Ventimask 60% was only marginally increased, at 31.7%. All the variable-performance masks, with the exception of the Hudson at 6 litre min^{-1}, produced nitrous oxide within the range 20–30%. Using nasal prongs, a minimum gas flow of 6 litre min^{-1} was required to achieve end-expired nitrous oxide concentrations of 20.0%; at 8 litre min^{-1} the concentration was 23.1%.

A check of the internal consistency of the measured concentrations was obtained theoretically on the basis that the delivered gas must be a mixture of the 1:1 nitrous oxide–oxygen with air. For each condition in tables I–III, a theoretical oxygen concentration was calculated from the measured nitrous oxide concentration (see Appendix). The calculated concentrations of oxygen were all a little less than the measured values (mean difference 1.9%, range 0.6–3.5%).

For the fixed-performance masks it was also possible to calculate the theoretical concentration of both oxygen and nitrous oxide, on the assumption that the fraction of driving gas in the delivered mixture is the same when the driving gas is nitrous oxide + 50% oxygen as when it is 100% oxygen (see Appendix). It was found that the expected concentrations of nitrous oxide were 12.0% and 24.7% for the 40% and 60% masks, respectively (table I). Thus the Hudson masks supplied less nitrous oxide than expected (6.5% and 20.4%, respectively), while the Ventimasks gave more (13.6% and 31.7%). This suggests that the differences were not the result of a systematic difference between the entrainment properties of our mixture and those of oxygen, but were features of the design of the two masks.

Hill [9] has shown that fixed-performance (low and high volume) masks are accurate up to a PIFR of 12 litre min^{-1}, but he found that they may be variable at greater PIFR. Our measurements using 100% oxygen as the driving gas showed predictable results at PIFR 20 litre min^{-1}. This apparent discrepancy may reflect the use of a lung model which cannot reproduce fully the interactions between masks and subjects.

In clinical practice, even during quiet breathing the PIFR may be as great as 30 litre min^{-1} [10]. Therefore the performance of the masks may be different in clinical use because the gas mixing and entrainment characteristics vary with flow rate [8].

APPENDIX A

To check the general validity of the measurements, the mutual consistency of measured nitrous oxide and oxygen concentrations for any given mask can be determined theoretically. Only a fraction (Fe) of the gas entering the lungs is the nitrous oxide–oxygen mixture, the remainder being air ($1-Fe$). Therefore, if $F\mathrm{N_2O}$ is the fraction of nitrous oxide in the gas and $F\mathrm{O_2}$ the fraction of oxygen, then:

$$F\mathrm{O_2} = (0.5Fe) + 0.21(1-Fe)$$

but

$$F\mathrm{N_2O} = 0.5Fe;$$

therefore,

$$Fe = 2F\mathrm{N_2O}$$

and hence

$$F\mathrm{O_2} = F\mathrm{N_2O} + 0.21(1-2F\mathrm{N_2O})$$
$$= 0.58F\mathrm{N_2O} + 0.21$$

For the fixed-performance masks, it is also possible to calculate the expected concentrations of nitrous oxide. Let $F\mathrm{d}$ be the fraction of driving gas in the mixture and ($1-F\mathrm{d}$) be the fraction of entrained gas. Then, for an x% mask, driven with oxygen and entraining air:

$$(F\mathrm{d} \times 1) + (1-F\mathrm{d})0.21 = x/100$$

therefore,

$$F\mathrm{d} = (x/100 - 0.21)/0.79$$

Hence, for a 40% mask, $F\mathrm{d}$ is 0.241 and for a 60% mask $F\mathrm{d}$ is 0.494. The mask, however, driven by 50% nitrous oxide+50% oxygen, entrains air; if we neglect any difference in the entrainment ratio which might arise from a change in the driving gas, the concentration of nitrous oxide delivered will be 0.5Fd—12% for the 40% mask and 24.7% for the 60% mask.

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CORRESPONDENCE

ACUPUNCTURE AND POSTOPERATIVE VOMITING IN CHILDREN

Sir,—For acupuncture analgesia to be developed from stimulation of an acupuncture point, an intact nervous system is required. It has been shown [1–3] that injection of local anaesthetic to the muscle beneath the acupuncture point abolishes and prevents the development of acupuncture analgesia. This abolition of acupuncture analgesia is related to the blocking of De Qi sensation. It is also accepted generally that acupuncture analgesia is of slow onset and long duration and there is therefore an induction period required for stimulation [4].

The paper by Yentis and Bissonnette [5] would therefore confirm both the need for an intact nervous system, as all their patients were anaesthetized before the acupuncture point was stimulated, and the need for an induction period.

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Sir,—The paper by Yentis and Bissonnette [1] concerning P6 acupuncture in children undergoing tonsillectomy raises several interesting points.

Dundee and colleagues [2] and Fry [3] have demonstrated that P6 stimulation (acupuncture needling, electroacupuncture or non-invasive acupressure) is an effective postoperative antiemetic in adults. Yentis and Bissonnette [1] suggest that children often respond well to acupuncture and are included in the group termed "strong reactors". However, their findings would suggest otherwise and are in agreement with the only other comparable study in children using P6 acupressure, in which a non-invasive stimulus was used 1 h before surgery [4] in order to overcome the objection of Dundee [5] that, for acupuncture (and presumably acupressure) to be effective, it must be applied before the emetic stimulus. Yentis and Bissonnette [1] indicated correctly that acupuncture was likely to be unacceptable to both children and parents before anaesthesia. Their children received 5 min of manual needling at the left P6 wrist point immediately after intubation of the trachea, but before the start of surgery. It may be argued that several emetic stimuli occurred before acupuncture was applied, including thiopentone, nitrous oxide and pharyngeal stimulation.

Only one study [6] has found P6 stimulation (acupuncture needling) to be ineffective in adults for treatment of postoperative emesis. This failure also may have been a result of the timing of acupuncture [5], as discussed above, or a result of the small number of subjects. Of all the quoted studies concerning P6 stimulation, only Yentis and Bissonnette [1] and Lewis [4] defined the "clinical antiemetic effect" (reduction in the incidence of vomiting from control to test groups) which the study was designed to detect, using power analysis [7] to link sample size, antiemetic effect and significance level. However, Dundee [2] indirectly compared P6 stimulation with antiemetic drugs, and found it to be as effective as metoclopramide 10 mg and cyclizine 50 mg, but less effective than droperidol 2.5 mg.

Finally, there is a high incidence of postoperative vomiting after discharge from hospital in children. Wilton and Burn [8] found that 56% of children receiving perioperative papaveretum vomited after discharge, within the first 24 h. The authors suggested that early ambulation and travel may have contributed to the incidence of emetic symptoms. Yentis and Bissonnette [1] recorded only the overall incidence of vomiting in the first 19.6 h (on average); it would have been interesting to record the incidence of vomiting at home. Lewis and colleagues [4] found a greater rate of vomiting at home than during the period within hospital among children undergoing outpatient strabismus correction; this finding was similar for both control and acupressure groups.

Current evidence suggests that P6 stimulation is ineffective as an antiemetic in children. Even if a small antiemetic effect can be demonstrated by large controlled studies, invasive acupuncture is unlikely to become popular because of the problems of acceptability and timing. Acupressure is clearly more acceptable in awake children; however, it appears to have a shorter duration of action compared with invasive methods in adults [2]. Children are unlikely to tolerate continuous, accurately applied, P6 acupressure over long periods as a treatment for late postoperative vomiting.

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Sir,—Thank you for the opportunity to reply to these letters.

Whilst the mechanism of acupuncture antiemesis is unknown, it would appear that acupuncture requires an intact nervous system, as suggested by Dr Nash, as it has been shown to reduce vomiting when administered before [1] and after [2], but not during [3], anaesthesia. In addition, Ghaly and Dundee reported that local anaesthetic infiltration of the P6 point prevented the antiemetic effect of stimulation [4].

With regards to an induction period, I have used P6 acupuncture in a few cases of acute travel sickness and gastroenteritis, and have found relief consistently to occur within a few minutes of stimulation, although it is often short-lived. This is similar to the rapid onset of relief that often follows acupuncture for other conditions.

As Lewis and Wilton state in their letter, invasive P6 acupuncture is unlikely to become popular in paediatric anaesthesia. Dundee's suggestion that the acupuncture must precede the emetic stimulus in order to be effective [1] is not supported by the study of Ho and colleagues, in which postoperative acupuncture significantly reduced vomiting after gynaecological surgery [2]. It is thus possible that anaesthesia suppresses the antiemetic effect of acupuncture (and that is more important than its timing), requiring administration to awake patients.

The aetiology of vomiting after strabismus surgery is likely to be different from that following tonsillectomy, and is thought to involve traction on the extraocular muscles or postoperative optokinetic imbalance [5]. In the study by Lewis and colleagues, morphine 0.1 mg kg^{-1} was administered i.v. to all patients and the incidence of vomiting was 82% and 94% in the control and treatment groups, respectively [6]. This compares with control group incidences of 41–60% in most previous studies [5, 7–9], although an incidence of 85% has been reported [10]. We have studied invasive P6 acupuncture administered after induction of anaesthesia in children undergoing strabismus surgery and found it to be the same as pretreatment with i.v. droperidol 0.075 mg kg^{-1}, although we suspect that this result demonstrates the inefficacy of droperidol in this situation rather than any efficacy of acupuncture, as the incidence of vomiting was high in both groups [11].

The incidence of vomiting after strabismus surgery may be under-reported if vomiting at home is not included, as patients usually stay in hospital for only a few hours. This is likely to be less of a problem with tonsillectomy, for which patients are routinely admitted overnight.

S. M. YENTIS
London

1. Dundee JW, Ghaly RG, Bill KM, Chestnutt WN, Fitzpatrick KTJ, Lynas AGA. Effect of stimulation of the P6 antiemetic point on postoperative nausea and vomiting. *British Journal of Anaesthesia* 1989; **63**: 612–618.
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4. Ghaly RG, Dundee JW. Are neural pathways involved in acupuncture antiemesis? *Irish Journal of Medical Science* 1980; **159**: 30.
5. Warner LO, Rogers GL, Martino JD, Bremer DL, Beach TB. Intravenous lidocaine reduces the incidence of vomiting in children after surgery to correct strabismus. *Anesthesiology* 1988; **68**: 618–621.
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9. Lerman J, Eustis S, Smith DR. Effect of droperidol

treatment should be effective whatever the aetiology of the symptom. In contrast, in TCM the treatment of the symptom depends on its aetiology. Thus the antiemetic effect of P6 in minor gynaecological surgery [2, 3] is logical because in this case postoperative vomiting may be primarily a result of the effect of the anaesthetic drugs. According to TCM, P6 would regulate the energy ("chi") of the "middle hearth" and would bring down the "Yin chi". However P6 may act only on hollow organs ("fu"). In surgical strabismus correction, the frequency of vomiting is particularly great, probably because of the peroperative manipulation of the eye and its muscles. Thus, in this situation, P6 may not be very effective as it does not act on the eye which is a full organ ("zang") located in the "superior hearth".

Knowledge of the TCM basis indicates that the following points might be more relevant: Bladder 10, (Tianzhu) which is a sedative point of the parasympathetic system; Bladder 11 (Dazhu), which strengthens the Yin energy of the eye; Gall-bladder 34 (Yanglingquan), which is the joining point of the energy of tendons and muscles. The dispersal of this point will diminish the parasympathetic stimulation resulting from surgical traction on the eye muscles.

P. VEROLI
V. ASTIER
Paris

1. Lewis IH, Pryn SJ, Reynolds PI, Pandit UA, Wilton NCT. Effect of P6 acupressure on postoperative vomiting in children undergoing outpatient strabismus correction. *British Journal of Anaesthesia* 1991; **67**: 73–78.
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3. Dundee JW, Ghaly RG, Bill KM, Chestnutt WN, Fitzpatrick KTJ, Lynas AGA. Effect of stimulation, of the P6 antiemetic point on postoperative nausea and vomiting. *British Journal of Anaesthesia* 1989; **63**: 612–618.

COMBINED SPINAL–EXTRADURAL ANAESTHESIA IN OBSTETRICS

Sir,—It is surprising how much information one may obtain on occasions from a small letter compared with a long article. I refer to the interesting letter of Dr Brownridge [1] concerning combined spinal–extradural anaesthesia in obstetrics. Dr Brownridge reported his surprise at having no postdural puncture headaches in about 1000 sections in 15 yr, and his explanation, the use of extradural pethidine in saline for up to 48 h after surgery is, I believe, correct. I wish to refer him to three letters in which I reported that I have treated postdural puncture headache with extradural morphine [2–4].

Incidentally, I should draw your readers' attention to the fact that the first report of combined spinal–extradural anaesthesia was

[redacted]

4. Eldor J. Treatment of post-epidural headache with epidural morphine injection. *Asian Archives of Anaesthesia and Resuscitation* 1991; **35**: 195–196.
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6. Eldor J, Chaimsky G, Olshwang D. Combined spinal–epidural needle (CSEN) for the combined spinal–epidural block. *Acta Anaesthesiologica Scandinavica* 1989; **33**: 617.
7. Eldor J, Brodsky V. Danger of metallic particles in the spinal–epidural spaces using the needle-through-needle approach. *Acta Anaesthesiologica Scandinavica* 1991; **35**: 461–463.
8. Eldor J, Chaimsky G. Combined spinal–epidural needle (CSEN). *Canadian Journal of Anaesthesia* 1988; **35**: 537–539.
9. Eldor J, Guedj P. Une nouvelle aiguille pour l'anesthésie medullaire combinée spinale–epidurale (AMCSE). *Annals Français d'Anesthésie et Réanimation* 1990; **9**: 571–572.
10. Eldor J, Gozal Y, Guedj P, Pode D, Cotev S. Combined spinal–epidural anesthesia with a specialized needle. *Regional Anesthesia* 1991; **16**: 348–349.
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USE OF DRUGS IN CHILDREN

Sir,—The problems of introducing new and potentially beneficial, but unlicensed, drugs into paediatric practice is underlined by the disclaimer published recently in your Journal [1]. Many drugs in regular use in adult practice are not licensed for use in children, and physicians face an ethical and possibly medico–legal dilemma if they wish to exploit the special benefits advertised for these agents in children in their care. This problem has existed for many years [2], and yet little has been done to improve the situation [3]. It seems that, after an agent has received its general licence, the hitherto overwhelming interest in developmental projects shown by the manufacturer dissipates rapidly, and requests for assistance with research are met by a polite refusal, usually on the grounds that newer compounds are taking precedence, or that paediatric research is ethically more difficult.

Surely, if a company believes its product is superior to its predecessors, then it should be duty bound to undertake adequate investigation to make this product available to all patients and physicians. Perhaps if licences were granted only to drugs which have been investigated across the age ranges, some of the apparent "ethical" difficulties could be overcome.

J. Stevens
Oxford

1. Rodgers E. Diprivan intensive care sedation in children. *British Journal of Anaesthesia* 1991; **67**: 505.
2. Shirkey H. Therapeutic orphans. *Journal of Paediatrics* 1963; **72**: 119–120.
3. Kaufmann RE. Fentanyl, fads and folly. *Journal of Paediatrics* 1991; **119**: 588–589.

HYPOXIA AFTER DENTAL ANAESTHESIA

Sir,—We were interested in the study by Dr Lanigan on oxygen desaturation after dental anaesthesia [1] and agree that hypoxia is a frequent occurrence after short outpatient dental procedures. He found also that the use of supplementary oxygen during recovery did not affect the incidence of desaturation. Dr Lanigan suggests that failure to recognize airway obstruction may be an important factor in the aetiology of these desaturations. We would agree that airway maintenance is essential to the avoidance of hypoxia at this time and we present further data to confirm this.

A study of the use of the laryngeal mask for dental outpatient anaesthesia has been published previously, but monitoring of oxygen saturation ceased at the end of the surgical procedure and no comment was made on the quality of recovery [2]. At the Dental Hospital in Manchester we have measured oxygen saturation during paediatric dental outpatient anaesthesia and have found that desaturation to less than 90 % is a common occurrence during recovery, when no supplementary oxygen is given. In 30 patients without an artificial airway *in situ*, six (20 %) became hypoxic. If a nasopharyngeal airway was used, one of 30 (3.3 %) became hypoxic before it was removed and seven (23.3 %) after its removal. However, if a laryngeal mask had been used, then only one of 80 (1.3 %) patients became desaturated before its removal and nine of 80 (11.3 %) after removal.

Thus 12.5 % of patients with a laryngeal mask desaturated during recovery, compared with 26.7 % with a nasopharyngeal airway and 20 % with no airway. These findings support the conclusion that airway obstruction is a cause of desaturation during recovery from dental anaesthesia, and that this may be reduced by the use of the laryngeal mask airway.

The finding that the incidence of desaturation was not significantly decreased by the use of supplementary oxygen should not lead to any recommendation that oxygen therapy is unnecessary. Dr Lanigan showed that minimum Sp_{O_2} was significantly less breathing air. Although supplementary oxygen is not a remedy for airway obstruction, it provides an increased margin of safety when obstruction occurs.

B. J. Woodcock
T. M. Young
Manchester

1. Lanigan CJ. Oxygen desaturation after dental anaesthesia. *British Journal of Anaesthesia* 1992; **68**: 142–145.
2. Bailie R, Barnett MB, Fraser JF. The Brain laryngeal mask. A comparative study with the nasal mask in paediatric dental outpatient anaesthesia. *Anaesthesia* 1991; **46**: 358–360.

Sir,—Drs Woodcock and Young support my suggestion that airway obstruction is a common cause of desaturation during recovery from dental anaesthesia and recommend the use of a laryngeal mask airway for this period. One could also recommend the use of a nasopharyngeal airway based on these data, and that both artificial airways should be left *in situ* until removed by the patient.

Given that desaturation in my study was almost twice as common with locum recovery nursing staff compared with permanent staff, irrespective of the use of supplementary oxygen, maintenance of a clear airway seems to me to be of cardinal importance. Supplementary oxygen should, of course, be immediately available, but it may *not* provide an increased margin of safety when obstruction occurs—if it delays detection of that obstruction. Furthermore, the increasing use of the laryngeal mask airway militates against training in the maintenance of a clear airway without artificial aids; this should be our prime concern.

C. Lanigan
London

MATERNAL AND FETAL HAEMODYNAMIC EFFECTS OF SPINAL AND EXTRADURAL ANAESTHESIA FOR ELECTIVE CAESAREAN SECTION

Sir,—We read with interest the article by Robson and colleagues [1]. Close analysis of the spinal group shows that, before any intervention, the average cardiac outputs were 6.73, 6.75 and 7.36 litre min^{-1} at 5, 10 and 15 min, respectively. There was no significant difference between basal and postspinal cardiac output, and at 15 min cardiac output was on average 400 ml greater. This questions why mothers who have the same average cardiac output before and after spinal anaesthesia gave birth to babies whose average umbilical pH at birth was as low as 7.22. One possible reason for this is that aorto–caval compression was still present in this group of patients.

Evidence to support this hypothesis is present if a comparison is made of total peripheral resistance (TPR) between the extradural and spinal groups: basal TPR was 1087 and 1031 dyne s cm^{-5}, respectively. However, after the institution of regional anaesthesia, the spinal group had consistently greater TPR. In fact, at 10 min (by which time one would expect full sympathetic block to be present in the spinal group but not in the extradural group) the TPR was 15 % greater in the spinal group. In addition, although skin incision–delivery times were recorded, uterine incision–delivery (U–D) time is a more sensitive measurement. With such small groups, prolonged U–D times in as few as two patients might adversely affect the average umbilical artery pH. Furthermore, it is not evident from the methods whether or not any of these patients received oxygen after institution of regional anaesthesia. Finally, in the same unit a study of 140 elective Caesarean section patients who received spinal anaesthesia with hyperbaric 0.5% bupivacaine 1.5–2.5 ml gave an average umbilical vein pH of 7.31 (0.04) and an umbilical artery pH of 7.26 ($\pm$0.04). In common with the study in question, all the patients received a preload of Hartmann's solution 1 litre followed by an infusion of ephedrine 60 mg in Hartmann's solution 1 litre to prevent hypotension. However, as suggested by Kang [2], the only difference was that these patients received a rapid infusion of ephedrine 10 mg in the first 2 min. We agree with the findings of Kang that the rapid infusion of ephedrine prevents hypotension and subsequent neonatal acidosis. Umbilical artery and vein pH in the 20 patients studied by Kang were 7.26 ($\pm$0.03) and 7.34 ($\pm$0.04), respectively.

In conclusion, we recommend the use of spinal anaesthesia using a combined spinal and extradural technique for both emergency and elective procedures in obstetrics. It provides both rapidity and density of spinal block, combined with the ability to extend the block and provide postoperative analgesia with the extradural catheter. Hypotension and subsequent neonatal acidosis can be prevented by rapid infusion of ephedrine and, as always, by ensuring adequate precautions have been taken to prevent aorto–caval compression.

M. Patel
A. Swami
H. Dent
London

1. Robson SC, Boys RJ, Rodeck C, Morgan B. Maternal and fetal haemodynamic effects of spinal and extradural anaesthesia for elective Caesarean section. *British Journal of Anaesthesia* 1992; **68**: 54–59.
2. Kang YG, Abouleish E, Caritis S. Prophylactic intravenous ephedrine infusion during spinal anesthesia for Cesarian section. *Anesthesia and Analgesia* 1982; **61**: 839–842.

Sir,—Thank you for sending me this correspondence. While we accept that mean cardiac output (CO) did not change in the spinal group, there were some patients who exhibited a profound decrease. This was the reason why we also reported the percentages changes in CO. We accept that aorto–caval compression could have led to a reduction in cardiac output in some patients, although every effort was made to prevent this. However, as the subjects were allocated randomly to the groups and the same preventative measures were undertaken in each group, we suggest the difference in pH is more likely to be secondary to the haemodynamic effects of spinal anaesthesia.

The umbilical artery data from the author's large series are reassuring. It would be interesting to know the number of babies with an umbilical artery pH $\leqslant$ 7.15. We agree that one possible reason for the differences between our results and those of Kang, Abouleish and Caritis [1] could have been the different ephedrine regimens used. This was pointed out in the discussion and is a topic we are presently investigating.

S. C. Robson
London

1. Kang YG, Abouleish E, Caritis S. Prophylactic intravenous ephedrine infusion during spinal anesthesia for Cesarian section. *Anesthesia and Analgesia* 1982; **61**: 839–842.

PREDICTION OF THE SPREAD OF REPEATED SPINAL ANAESTHESIA WITH BUPIVACAINE

Sir,—The paper by Tuominen and colleagues [1] is based on an interesting series of patients who underwent repeated spinal anaesthesia. On the first occasion, all the patients received plain bupivacaine, but subsequently a modified technique was used, with the patients being allocated to three groups. The first group had blocks to T10 or below on the first occasion and the second group had blocks above that level. During the second anaesthetic, the technique was changed in an attempt to increase the level of block in the first group and decrease it in the second. The changes in technique produced significant alterations in the level of block in the groups as a whole, although it has to be noted that there were individual exceptions in whom the result was the opposite to that "expected". These results represent a nice demonstration both of the way in which the anaesthetist may influence events in spinal anaesthesia, and of the way in which it can frustrate his best intentions!

The third group of patients had developed a very wide range of blocks on the first occasion. During the second anaesthetic, an identical technique was used but hyperbaric, rather than plain, bupivacaine was injected. There were no differences between the two blocks in the group as a whole, although various levels of injection, patient position and needle size were used. The result is used to justify the conclusion that density of solution is relatively unimportant in determining intrathecal drug spread. As the vast body of literature on spinal anaesthesia takes the opposite view, I cannot accept this conclusion. Any technique, even when applied meticulously by a single individual, would produce a range of blocks. When such basic factors are not kept constant, they may obscure the influence of other factors, even one as fundamental as baricity. It is essential in studies of spinal anaesthesia that the only difference between two groups should be the one under investigation, so that its effect is clear.

J. A. W. Wildsmith
Edinburgh

1. Tuominen M, Pitkänen M, Taivainen T, Rosenberg PH. Prediction of the spread of repeated spinal anaesthesia with bupivacaine. *British Journal of Anaesthesia* 1992; **68**: 136–138.

Sir,—We thank you for the opportunity to reply to Dr Wildsmith's letter.

Because of limited space in this section, we refer directly to group 3 in our study. Dr Wildsmith may have misinterpreted our methods. We collected repeated spinal anaesthetics for three groups, each of which could have been a separate study. In group 3 the only difference between the first and second spinal anaesthetic was the baricity of bupivacaine; otherwise, the technique was similar in each patient: the level of injection, patient position and needle size, and the volume of the local anaesthetic solution or speed of injection. In the two other groups, the technique for the first and second spinal anaesthetics was different because of the different aims: to produce a higher or lower block. In this study each patient served as his own control, and this should serve as a reliable method in a clinical study. We compared the changes within the groups, but not between groups 1, 2 and 3. The only way to overcome the problem of a wide range of blocks would have been to discard results from some patients, but that did not seem reasonable.

Our conclusion was not "density of solution is relatively unimportant". We stated: "Individual anatomical properties may play a more important role than expected in the subarachnoid spread of local anaesthetic"...and, "The extent of block is affected also by the baricity of the solution in relation with the position of the patient."

The conclusion stems also from the studies by Stienstra and van Poorten [1], Mitchell and colleagues [2] and Alston [3] in which no differences between the spinal blocks with plain and hyperbaric 0.5% bupivacaine were found. Those studies demonstrated nicely that there are always patients who have a low block and others with unnecessarily high spread of analgesia, irrespective of the density of the local anaesthetic solution used.

We drew our conclusion on the basis of the results in all three groups of this study, our earlier study of repeated spinal anaesthetics and the findings by Mitchell and colleagues [2] and Stienstra and van Poorten [1].

We do appreciate the vast literature on regional anaesthesia in addition to the concepts drawn from recent studies. However, we are also prepared to accept new opinions on the prediction of spread of spinal anaesthesia. We feel that what is needed most at this stage is greater knowledge of the anatomical–physiological determinants of the individual patient.

M. Tuominen
M. Pitkänen
T. Taivainen
P. H. Rosenberg
Helsinki

1. Stienstra R, van Poorten JF. Plain or hyperbaric bupivacaine for spinal anesthesia. *Anesthesia and Analgesia* 1987; **66**: 171–176.

2. Mitchell RWD, Bowler GMR, Scott DB, Edström HH. Effects of posture and baricity on spinal anaesthesia with 0.5% bupivacaine 5 ml. *British Journal of Anaesthesia* 1988; **61**: 139–143.
3. Alston RP. Spinal anaesthesia with 0.5% bupivacaine 3 ml: comparison of plain and hyperbaric solutions administered to seated patients. *British Journal of Anaesthesia* 1988; **61**: 385–389.

POSTDURAL PUNCTURE HEADACHE

Sir,—We read with interest the article by Lynch and colleagues [1] comparing the incidence of postdural puncture headaches (PDPH) associated with 22-gauge and 25-gauge Whitacre needles.

As mentioned in the accompanying editorial, a significant factor affecting the incidence of PDPH is age. Lynch's group examined patients over a wide age range (15–81 yr). We feel that to include within the same group patients with such a well recognized difference in the incidence of PDPH, is inappropriate.

Lynch and colleagues attempted to subdivide their patient groups further, but considering the previously demonstrated incidence of PDPH of less than 4% (as stated by the authors) in younger patients [2, 3], the number of patients needed to demonstrate a significant difference ($P < 0.05$) in PDPH, even in this susceptible group, would have to be much greater. We feel that it is important to stress that the stated result that there was "no significant difference between groups" does not mean that the 22-gauge and 25-gauge Whitacre needles have clinically equivalent incidences of PDPH. Knowing the number of patients studied and the expected incidence of PDPH, there is a greater than 50% chance of finding no difference between the two needles if, in fact, this is not the true situation.

On examination of the published data, we were unable to reconcile the stated incidence of 0.9% for PDPH in females older than 45 yr with the detailed patient characteristics shown in table III. Clarification would be helpful.

It is important and clinically relevant to discover if a 25-gauge Whitacre needle has significant advantages over a 22-gauge and we hope that Dr Lynch and his colleagues are continuing their study so that this question may be answered.

C. M. Cooney
J. Tarpey
Dublin

1. Lynch J, Krings-Ernst I, Strick K, Topalidis K, Schaaf H, Fiebig M. Use of a 25-gauge Whitacre needle to reduce the incidence of postdural puncture headache. *British Journal of Anaesthesia* 1991; **67**: 690–693.
2. Kreusher H, Sandmann G. Relief of headache following spinal anaesthesia by use of the Whitacre cannula. *Regional Anaesthesie* 1989; **12**: 46–49.
3. Sami HM, Skaredorf MN. In hospital incidence of post lumbar puncture headache in Caesarean section patients associated with the 22 G Whitacre needle. *Regional Anaesthesia* 1989; **14**: 44.

Sir,—Thank you for the opportunity to respond to the letter from Drs Cooney and Tarpey. As the authors stated, the age factor in the aetiology of postdural puncture headache (PDPH) is indeed important, but as our study was designed also to look at the handling characteristics of the 25-gauge Whitacre needle, we feel that the inclusion of all age groups in the study was justified. Younger patients were still well represented in the study, however, as some 66% of the patients in both groups were younger than 40 yr (M:F = 2:1).

We agree with Drs Cooney and Tarpey on the importance of enrolling sufficient numbers of patients to assess statistical significance. As the incidence of PDPH becomes less (1–2%), only the prospective evaluation of PDPH in a large series of patients of matched sex, age and medical background, using matched techniques for matched surgical procedures will resolve these questions [1, 2]. The design of large multicentre studies with appropriate patient numbers, although beset with difficulties for a variety of logistical and historical reasons, may be one possible solution to this problem. We are exploring these possibilities at present, while still continuing our studies with Whitacre needles.

We agree also that the lack of a statistically significant difference in the incidence of PDPH between the groups does not necessarily mean that they will have a clinically equivalent incidence of PDPH. Preliminary reports from other authors using a Whitacre 25-gauge needle in large groups of patients have confirmed their ability significantly to reduce the incidence of PDPH without compromising the ease of administration of spinal anaesthesia [3]. The incidence of 0.9% refers to the incidence of PDPH in young males and not older female patients as the authors mistakenly assume.

J. Lynch
Seattle

1. Reid JA, Thorburn J. Headache after spinal anaesthesia. *British Journal of Anaesthesia* 1991; **67**: 674–677.
2. Dixon CL. The Sprotte, Whitacre and Quincke spinal needles. *Anesthesia Review* 1991; 5: 42–47.
3. Hurley RJ, Hertwig LM, Johnson MD, Datta S. Incidence of postdural puncture headache in the obstetric patient: 25 gauge Whitacre *vs* 26 gauge Quincke tip needles—a preliminary report. In: Proceedings of the Society of Obstetric Anesthesia and Perinatology, Boston, 1991.

ADEQUACY OF PREOPERATIVE SAFETY CHECKS OF THE BAIN BREATHING SYSTEM

Sir,—Recently, we discovered a large crack in the fresh gas supply to a Bain breathing system—a well known, but infrequently encountered, complication. The leak was discovered by a simple occlusion test of the inner (fresh gas flow) tube—a test which should be known to, and used by, all anaesthetists.

Following a visual check, the circuit was pressurized, the bag inspected for leaks and the expiratory valve opened and checked. The oxygen flush was activated; the reservoir bag failed to deflate. A 6-litre min^{-1} fresh gas flow was commenced and the inner tube occluded using a finger (a 2-ml syringe plunger may be used). The flowmeter bobbin failed to descend, indicating a leak from this part of the circuit. Close visual inspection revealed no obvious fault, but when the system was dismantled, the inner mount of the co-axial manifold was found to be sheared.

Reliance on the Venturi test does not necessarily detect leaks that occur in the distal part of the circuit. The only reliable test is to occlude the inner tube and to observe if the transmitted back pressure causes the flowmeter bobbin to descend. Reliance on pulse oximetry, or on end-tidal carbon dioxide monitoring, would provide a late indication of impeding disaster.

We surveyed all the 30 full-time anaesthetists working at our group of hospitals. This included 16 consultants, two senior registrars, six registrars, and six senior house officers. Staff grades and clinical assistants were excluded from the survey. Of the 30 anaesthetists surveyed, only 14 (47%) knew of the correct test and, of these, only nine (30%) used it. The reason for this was that they relied on sophisticated monitoring to detect apparatus failure.

The results of this survey suggest the teaching of safety checks of the Bain system may be deficient, and that anaesthetists are lulled into a false sense of security by sophisticated monitoring techniques. Furthermore, this deficiency was not confined to junior grades.

Although this small survey is not representative of the profession as a whole, it is representative of anaesthetists at our group of hospitals, and may well apply to other institutions.

A. R. Williams
G. Van Hasselt
Poole, Dorset

British Journal of Anaesthesia 1992; **68**: 639

BOOK REVIEWS

Obesity and Cachexia—Physiological Mechanisms and New Approaches to Pharmacological Control. Edited by N. J. Rothwell and M. J. Stock. Published by John Wiley & Sons, Chichester. Pp. 304; indexed; illustrated. Price £60.

This volume is the result of a meeting held at the Royal Institution in the spring of 1990 under the auspices of the Biological Council. It brought together several leading workers in the field of metabolism, specifically those active in research into obesity and metabolic responses to trauma and disease. The book is a collection of papers written by the various presenting authors; there is no record of any discussion. As such, it is an excellent review of the biochemical and metabolic mechanisms that control body mass and composition, and the ways they are altered in obesity, cancer and infection. The emphasis, however, is scientific: much of the work described is in animals rather than man, and this is reflected in the fact that most of the authors are scientists, with relatively few clinicians.

Mike Stock starts with a wide ranging but unreferenced review of both areas. There follow chapters on central control of energy intake (Liebowitz) and of thermogenesis (Rothwell), on protein metabolism and regulation of muscle mass (Rennie), insulin metabolism in obesity and wasting disorders (Frayn), the role of the sympathetic nervous system in obesity (Astrup), cancer and cachexia (Lundholm) and metabolic rate after injury (Little)—and so on. There is nothing about wasting of intensive care patients and what strikes one throughout is that there is next to no documentation on rates of wasting as measured in patients.

Pharmacological aspects again appear to be restricted to their use in animal models to elucidate biochemical mechanisms rather than as therapeutic agents, although in his summing up Don Stribling does mention briefly the possibilities of clenbuterol in the maintenance of lean body mass, and the beta$_3$ agonist produced by Beecham, which does appear to be effective in increasing metabolic rate in obesity.

In short, *Obesity and Cachexia* is a superb review of the metabolism of energy balance and the pharmacological possibilities for its control, but has little to offer the practising clinician. However, this is a reflection more of the state of the subject itself than of any policy on the part of the editors and organizers of the symposium.

I. T. Campbell

General Anaesthesia and Sedation in Dentistry, 2nd Edn. By C. M. Hill and P. J. Morris. Published by Butterworth–Heinemann Ltd, Oxford. Pp. 157; indexed; illustrated. Price £16.50.

This is the 2nd Edition (1st Edition, 1983) of a book with a targeted audience of dental students and also dental practitioners interested in anaesthesia and sedation. As is apparent from the title, both general anaesthesia and sedation are described. The book has 10 chapters which deal with patient assessment, pharmacology, i.v. and inhalation anaesthesia, monitoring, relative analgesia, i.v. sedation, tracheal intubation and emergencies. Each subject is addressed in a logical manner at a level appropriate to undergraduate teaching. Most subjects are dealt with comprehensively. However, I felt that two areas required more detail than is provided: recovery, and assessment before discharge. The area of postoperative care and analgesia is not mentioned.

I was surprised to note, in the section on i.v. technique, that the authors appear to condone the use of a single injection with a needle in the antecubital fossa—a practice long abandoned by most anaesthetists. The Poswillo report will have a major effect on all aspects of dental anaesthesia and sedation, including teaching. The report is mentioned only once in the text, where it is referred to as a report on sedation. It is unfortunate that the recommendations of this report with regard to monitoring, and those of the Association of Anaesthetists, are not discussed in the chapter on monitoring.

Overall, this will be a useful book for dental students and those involved in teaching dental anaesthesia.

C. S. Reilly

The Principles and Practice of Pharmacology for Anaesthetists, 2nd Edn. By T. N. Calvey and N. E. Williams. Published by Blackwell Scientific Publications, Oxford. Pp. 522; indexed; illustrated. Price £49.50.

The first edition of this book (published in 1982) was outstanding, and it has been my pleasure to review the second edition, which is undoubtedly even better. In addition to updating and improving many of the existing chapters, the book contains new chapters on variability in drug response, antihypertensives and anticoagulants.

In my opinion, there is no superior and more comprehensive explanation of the principles of pharmacology as applied to anaesthesia than is found in this textbook. The first chapter deals with the principles of drug absorption, distribution and elimination, and all worked examples are relevant to anaesthesia. The chapter dealing with pharmacokinetics has wonderfully clear descriptions of the concepts of clearance, half-life and compartmental modelling. Any F.R.C.Anaes. candidate who does not understand these principles after reading this chapter should be advised to change career. Throughout the book, but in this chapter especially, there are many imaginative tables and graphs.

The pharmacodynamics chapter is excellent also and the description of partial agonists particularly good. Again, all the practical examples used to demonstrate each principle involve drugs used in anaesthesia. The subject of drug interactions in anaesthesia is covered relatively well, but it is slightly disappointing in that the references are not particularly recent. However, it is still extremely well written and relevant.

After describing basic principles, the authors embark upon a systematic description of drugs used in anaesthesia. I.v. agents are covered very well indeed and, again, there is excellent use of tables, comparing properties of each agent. This is of major assistance to candidates studying for examinations. In addition to a general description and comparison of the volatile agents, there is an excellent and refreshing description of the basic principles involved in the pharmacology of volatile agents. This chapter is particularly well written, and includes the pharmacology of desflurane.

Chapters concerning local anaesthetics and drugs acting on the neuromuscular junction follow. Again, these are very well written and comprehensive. One of the best chapters in the book is that describing analgesic agents. It gives an excellent description of opioid receptors and their pharmacology and there is considerable space given to non-steroidal anti-inflammatory drugs. The book concludes with chapters describing drugs acting on the autonomic nervous system, sedatives and antiemetics, hypotensive agents, antiarrhythmic therapy, anticoagulants and hypoglycaemic drugs. These, again, are very comprehensive and well written, but I found discussion of agents used in hypotensive anaesthesia rather brief.

In summary, this is one of the best anaesthetic textbooks currently available. It is a delight to read and should, in my opinion, be the property of every trainee anaesthetist and in the library of every anaesthetic department. It is highly recommended indeed to all candidates sitting the F.R.C.Anaes. Part 2 examination.

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SUPPLEMENT ON POSTOPERATIVE NAUSEA AND VOMITING

Editors: G. SMITH
D. J. ROWBOTHAM

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INTRODUCTION

The most common and distressing symptoms which follow anaesthesia and surgery are pain and emetic problems. Clearly, under most circumstances, pain causes the greater amount of suffering, particularly after major surgery, but in some instances nausea and vomiting may be more distressing, particularly after minor surgery. In day-case surgery, emesis may also have important economic implications, for example, admission to inpatient beds because of intractable vomiting.

In the past two decades, pain after surgery has been subjected to an enormous amount of investigation and undoubtedly, major advances have been made in the management of this symptom; in the general anaesthetic journals, papers on pain management frequently preponderate over all other areas of anaesthetic research. Official reports on improving pain management have emanated from bodies responsible for the setting of standards in anaesthetic practice, for example the Report on Pain after Surgery from the Royal College of Anaesthetists and Royal College of Surgeons [1]. In contrast, postoperative nausea and vomiting have received less attention.

There is an extensive literature which touches upon or incorporates data on postoperative nausea and vomiting. Unfortunately, these data are frequently difficult to interpret and compare because of the methodology used and this may explain the relative shortage of major review articles in this area; an interval of eight years separating the two largest reviews of postoperative emesis [2–4]. In this supplementary issue of the *Journal*, we have attempted to provide the most comprehensive and up-to-date review yet available on the subject of postoperative nausea and vomiting (PONV). We commence with a broad picture of the physiological mechanisms underlying the causes of nausea and vomiting in the perioperative period and this is followed by a description of the methods involved in studying PONV. It will be clear from this article why it is so difficult to compare much of the literature in this field, and the difficulty in drawing conclusions from the extensive literature which spans several decades of anaesthetic practice. Subsequently there follow articles on surgical and patient factors in PONV, PONV in day-case surgery, and anaesthetic factors which are thought to contribute to this condition. Current methods of managing PONV are described in a comprehensive review.

One of the stimuli to enhanced recent interest in the problem of postoperative emesis is the introduction of the 5-HT_3 antagonists and their astounding efficacy in the management of vomiting induced by cancer chemotherapy. We therefore review the role of 5-HT in producing postoperative emesis, and finally there is a description of the results of recent studies on the use of 5-HT_3 antagonists on PONV.

In order to provide a full and comprehensive review, we have elected to subdivide the topic of PONV into eight sections. Clearly these divisions are somewhat arbitrary and it is therefore inevitable that there is some overlap between the articles in this issue. However, we regard an element of repetition not only as inevitable but indeed desirable; each article is relatively self-contained and therefore may be read separately.

We are grateful to Glaxo Group Research Ltd who have financed entirely the cost of the production and distribution of this supplement.

D. J. Rowbotham and G. Smith
Editors

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PHYSIOLOGY OF NAUSEA AND VOMITING

P. L. R. ANDREWS

INTRODUCTION: WHY IS THE MECHANISM NOT KNOWN?

Nausea and vomiting have been associated for many years with the use of general anaesthetics for surgical procedures, and descriptions of these side effects, induced by ether and chloroform, were included in the earliest textbooks of pharmacology and therapeutics. One of the first extensive descriptions of the phenomenon was by John Snow, published in 1848, within 18 months of the introduction of anaesthesia into Britain [93]. He observed that vomiting was more likely to occur if the patient had eaten recently. In most cases the vomiting lasted only a few minutes but in some it continued for hours or even days. He suspected that movement shortly after operation may have triggered the vomiting. Postoperative treatment included wine (which he considered more beneficial than smelling salts!) and Battley's solution of opium.

There has been a general trend towards a decrease in the incidence and intensity of the problem because of the use of less emetic anaesthetic agents, improved pre- and postoperative medication (e.g. analgesics), refinement of operative technique and identification of patient predictive factors [33]. However, in spite of these advances, nausea and vomiting still occur with unacceptable frequency in association with surgery and anaesthesia and the description of it as "the big little problem" [56] encapsulates much of the general perception. Although anaesthetics have been used to facilitate surgical procedures for almost 150 years, why is the mechanism of nausea and vomiting not known? This probably reflects at least four factors.

The complexity of the problem. Careful clinical studies of the phenomenon should give important clues to the mechanism but a consideration of the variables shows how difficult it may be to get other than some general indications. If we take a simple example using two patient variables (age, gender), three operative site variables (head and neck, abdomen, other), two premedication variables and three different anaesthetics, then the number of possible combinations is 36. It is clear, therefore, that to identify a mechanism or to assess the effects of an intervention on emesis requires a considerable number of patients in well controlled trials.

Inadequate quantification of the phenomenon. Although there have been a large number of clinical trials, in general the phenomenon has been poorly quantified; many studies fail to distinguish between nausea and vomiting, or retching and vomiting, although in most, but not all, of the more recent studies these variables have been fully quantified. In addition, until recently there was little detailed information on the time course of postoperative nausea and vomiting (PONV), a particularly useful source of clues about mechanisms.

Inadequate antiemetic regimens. Although emesis is a common symptom of disease, a side effect of many therapies (e.g. cytotoxic chemotherapy, radiotherapy, L-dopa) and a result of "natural" stimuli (e.g. motion, pregnancy), the physiology of emetic mechanisms has not been an area of particularly intense research since the classical studies of Wang and Borison in the late 1940s and 1950s [102–104]. Interest in basic mechanisms has been rekindled in recent years because attention has focused on the particularly distressing nausea and vomiting induced by anticancer chemotherapy. Additionally, the success of 5-hydroxytryptamine-3 (5-HT_3) receptor antagonists (e.g. ondansetron and granisetron) in treating this emesis has provided critical insights into the pathways involved in this form of emesis [8]. If 5-HT_3 receptor antagonists are found to be as effective against PONV as they are against anticancer therapies then it may at last be possible to identify the predominant mechanism involved.

Animal models. One major factor that has limited physiological and pharmacological studies of the mechanism of PONV is the apparent lack of a suitable animal model. Many of the common laboratory species such as rats and rabbits do not vomit irrespective of the stimulus, although they appear to exhibit "behavioural equivalents" of nausea. Carnivores (cat, dog and ferret) and laboratory primates (monkey, marmoset), as far as is known, respond to virtually the same range of emetic stimuli as man, including cytotoxic drugs and radiation, although there are considerable species differences in sensitivity. However, these species do not appear to

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suffer from pregnancy sickness, and postoperative and postanaesthetic emesis is not a commonly encountered problem. When PONV is encountered, it can often be ascribed readily to the premedication (e.g. morphine) or to the particular surgical procedure, although again there are species differences. For example, vomiting is not an uncommon sequelae to truncal vagotomy in the dog (and man) but is rare in the ferret [Bingham and Andrews, unpublished observation]. Perhaps it is not surprising that animals do not have PONV as experimental and even veterinary surgery do not mimic the entire clinical experience of a patient undergoing elective or emergency surgery.

Whatever the reason for the apparent differences between man and animals, the lack of an appropriate model has certainly hampered identification of mechanisms and hence the design of rational therapies based upon such an understanding. As a result, the tendency in PONV research has been to undertake clinical trials of agents whose antiemetic activity has been demonstrated against other stimuli such as motion (e.g. atropine) or gastrointestinal motility disorders (e.g. domperidone, metoclopramide). This approach continues with the trials of the 5-HT_3 receptor antagonists such as ondansetron (Zofran) which have been demonstrated to be effective to date against cytotoxic chemotherapy and radiotherapy-induced emesis [6, 37].

Taking these limitations into account, this review attempts to identify the specific mechanisms by which premedication, surgery and anaesthetics may activate the emetic reflex. Although the review is highly speculative in parts, the mechanisms proposed are, in general, testable. Before discussing the afferent, integrating and motor mechanisms of the reflex, it is perhaps worth reviewing nausea and vomiting in a more general biological than clinical context.

NAUSEA AND VOMITING IN BIOLOGICAL AND CLINICAL CONTEXTS

Definitions and functions

Nausia is an unpleasant, but not painful, sensation referred to the pharynx and upper abdomen, associated with a desire to vomit or the feeling that vomiting is imminent. It may be brief or prolonged, often occurring in "waves" and precedes vomiting or occurs in isolation. Vomiting may actually alleviate the sensation of nausea.

Vomiting is the forceful expulsion of upper gastrointestinal contents via the mouth and is usually, but not always, preceded by retching where no expulsion takes place but which involves activation of the same muscle groups (see below). Vomiting should not be confused with gastro-oesophageal reflux or regurgitation, neither of which is forceful nor involves the same pattern of muscle activation as retching and vomiting.

Nausea and vomiting are most often regarded clinically as undesirable side effects but in the natural world they have specific functions contributing to the survival of the animal. In the obligatory functions of eating and drinking, as with breathing, the body exposes itself to toxins [38]. The senses of vision, taste and smell are all used to provide information about food before swallowing, but many poisons are not bitter tasting, foul smelling or brightly coloured and so may not be identified by these senses that may be regarded as the first line of defence. After the contaminated food has passed the upper oesophageal sphincter, it can only be removed from the body rapidly by vomiting or possibly by diarrhoea. For the toxin to be ejected it must first be recognized as such, and this occurs by detectors in the lumen of the upper gut (pre-absorptive) and the circulation (post-absorptive). These detectors trigger a series of events which may be summarized and rationalized as follows: (i) nausea to stop further ingestion and to facilitate the development of a learned aversion so that the food is rejected before ingestion when encountered again; (ii) gastric relaxation to reduce gastric emptying of the contaminated food and intestinal retroperistalsis to return any contaminated food to the stomach; and (iii) retching and vomiting to purge the stomach.

Viewing nausea and vomiting from this perspective has implications for the way they are regarded in the clinic. First, as far as can be ascertained, the vomiting reflex evolved as a defensive reflex centred around the gastrointestinal tract. Mechanisms for the ejection of contaminated food are found throughout the animal kingdom, ranging from invertebrates, such as the starfish, to vertebrates including fish (e.g. trout, sharks and tuna), amphibia (e.g. frog) and birds (e.g. seagull, hawk), although the motor mechanism differs somewhat from that used by mammals. For vomiting to be evoked in any species, all that is needed is that the stimulus triggers one of the detection systems: there is no requirement for a specialized system for each type of stimulus. Second, the nausea and vomiting evoked by contaminated food is considered to be "appropriate" in that it leads to expulsion of the driving stimulus but in most clinical contexts the nausea and vomiting are "inappropriate" and have several additional adverse effects which are outlined below.

Consequences of PONV

If PONV was without detrimental effects to the patient, either real or potential, then there would be less pressing need to identify the mechanism and design therapies. However, this is clearly not the case and the effects of nausea and vomiting may be even more extensive than is at first appreciated. They may be classified into three types.

Physical. Retching and vomiting are fairly violent and intense physical acts and as such may place considerable stress upon certain structures, even in healthy subjects, particularly if protracted. These include oesophageal tears, possibly resulting in haemorrhage (Mallory–Weiss syndrome) and rupture of the oesophagus (Boerhaave syndrome), rib fracture, gastric herniation, muscular strain and fatigue, and rupture of cutaneous vessels in the upper body. The occurrence of these in association with PONV is unlikely because of its usually mild and brief nature, but this list serves to illustrate the forces involved in vomiting and why vomiting may cause wound dehiscence, intraocular bleeding and bleeding of skin flaps in the upper body after plastic surgery [94, 100].

The major physical problem associated with vomiting in the postoperative period is aspiration of vomitus and the triggering of cardiorespiratory reflexes. A component of the motor programme of the vomiting reflex ensures that the airways are protected but, because of the effect of anaesthesia, reflex coordination may be impaired in some patients. Similar problems may occur after over-indulgence with alcohol or in patients with damage to the brain stem. The mechanism underlying the failure of this automatic protective reflex for the airways is unclear but suggests a differential effect of anaesthetics on brain stem neurones. Under even deep surgical anaesthesia, animals and man continue to breathe spontaneously but vomiting is rare. During vomiting the intrathoracic pressure exceeds atmospheric because of transmission of increased intra-abdominal pressure to the thorax, thus for aspiration of vomitus to occur there must be stimulation of inspiration and opening of the glottis during this expulsive phase. In addition to failure of the coordination mechanism, there may also be depression of the mechanism that usually increases the level of arousal before vomiting.

Metabolic. The metabolic consequences of vomiting have been described extensively and include anorexia, dehydration and alkalaemia. These metabolic effects tend to occur when there is prolonged vomiting and are unlikely to be a problem in PONV as it is usually of short duration.

Psychological. The psychological impact of nausea and vomiting associated with anticancer chemotherapy and radiotherapy has long been recognized but PONV may also have such effects. Nausea is a very aversive stimulus and if induced by a particular food may induce a life-long aversion to that food [80]. This aversion is appropriate and forms part of the body's defence mechanism against poisonous foods. In the context of surgery, the nausea (and vomiting) are associated with the operative experience and may induce an aversion to further surgery, although for most patients this is unlikely to be a problem as multiple experiences of surgery are not common in the life of an individual. In addition, if a patient experienced PONV on one occasion, there may be an expectation that it may occur with subsequent surgery. In one study, the incidence of PONV was three times greater in patients who had previous experience of PONV [81]. This suggests that the sensitivity of the emetic reflex may be altered by higher inputs, although the pathways involved are not defined. This observation has a broader implication as it may suggest that the sensitivity of an individual to a particular emetic stimulus is contributed to by their previous emetic history. This may account for the increased incidence of nausea and vomiting after surgery, anticancer therapy with cytotoxic drugs and pregnancy in patients who are sensitive to motion stimuli. If the emetic pathways become sensitized to other stimuli by motion, there is no reason why there should not be cross-sensitization between other stimuli.

WHY DO POSTOPERATIVE NAUSEA AND VOMITING OCCUR?

The section above has emphasized that nausea and vomiting are natural responses that may be regarded as components of the body's defence system against ingested toxins: why then should anaesthesia and surgery induce nausea and vomiting? The reason does not lie in the fact that there is anything particularly special about anaesthesia and surgery but that, as with so many clinical situations in which nausea and vomiting occur, some feature of this treatment is capable of activating the emetic detectors. Thus it is not necessary to propose specialized detectors for each type of stimulus but only to show how the stimulus under consideration activates one of the triggers for the system. The logic of this approach is apparent when we consider that the vomiting reflex is present in animals that evolved long before medicine originated: the detectors that trigger the reflex evolved to identify potentially hazardous features of the natural and not the clinical environment. A similar argument can be proposed for motion sickness which, although it can be induced by riding some animals (e.g. camel), is associated most usually with man-made forms of transport.

The vomiting induced by contaminated food present in the gut lumen is appropriate as it leads directly to the ejection of the stimulus and as such is self-limiting. In contrast, many clinically relevant emetic stimuli are located in the plasma and, although they may trigger vomiting, the stimulus remains, contributing to the protracted nature of the emetic response seen with some drugs.

Although in broad terms we can say "why" anaesthesia and surgery can induce nausea and vomiting, the question "how" is much harder and as yet we do not have a satisfactory answer, even though it is possible to identify several of the most likely possibilities. Before discussing these specific mechanisms, the basic mechanisms of emesis will be reviewed briefly to provide a framework for discussion.

GENERAL MECHANISMS OF EMESIS

Three major components comprising the vomiting reflex can be identified: emetic detectors, integrative mechanisms and motor outputs. These will be discussed separately.

Emetic detectors

The key question that must be addressed is how the various components that may contribute to PONV, such as opioid premedication, the anaesthetic and surgical manipulation, trigger detection systems that have evolved primarily to detect ingested toxins? The section below describes the main ways in which the emetic system is stimulated and the way in which the stimuli relevant to PONV may cause activation are discussed in the sections that follow.

Abdominal visceral afferents. As the major function of the vomiting reflex is to protect against the accidental ingestion of toxins in the food, it is not surprising that the gut should have detection systems capable of activating the reflex. Indeed the gut afferents may be viewed as the second line of defence against poisoning via food if it has circumvented detection by vision, taste and smell which represent the first line [38]. The vagus is the major nerve involved in the detection of emetic stimuli and in its abdominal course contains about 80–90% afferent fibres. Electrical stimulation of the abdominal vagal afferents is capable of inducing emesis within 20 s, thus illustrating the potential of the pathway for rapid ejection of gastric contents (6). Two types of vagal afferent fibre are involved in the emetic response: (i) mechanoreceptors, located in the muscular wall of the gut are activated by both contraction and distension of the gut [4, 49]. Distension of the gastric antrum (e.g. by over-eating) or proximal small intestine (e.g. by obstruction) may induce nausea and vomiting by stimulation of these afferents; (ii) chemoreceptors, located in the mucosa of the upper gut, monitor several features of the intraluminal environment. They respond to mucosal stroking, acid, alkali, hypertonic solutions, temperature and irritants (e.g. copper sulphate) [4, 48, 49]. As lesion studies have shown that the emesis induced by intragastric hypertonic sodium chloride and copper sulphate is reduced or abolished by vagotomy, it is likely that it is these mucosal afferents that are responsible [6, 104]. Emesis induced by intraluminal bacterial toxins, such as staphylococcal enterotoxin, can also be abolished by vagotomy [96] and it is probable that such agents can also activate the mucosal vagal afferents, although this has not been studied formally.

The substrate for the polymodal mucosal chemoreceptor is not known but the current hypothesis suggests an arrangement rather like that in the taste buds or carotid body with a "detector cell" responding to a range of stimuli and releasing a neurotransmitter to discharge an afferent terminating in close proximity. In the intestine, the enterochromaffin cell has been proposed as the detector cell, although this awaits experimental confirmation.

Area postrema. The studies of Wang and Borison [102–104] brought about a major change in understanding the way in which emetic agents were detected and subsequently triggered the vomiting reflex. It had long been known that emesis could be induced by application of chemicals to the dorsal surface of the brain stem and it was assumed that this was through direct stimulation of the vomiting centre, thought to be located in this region. However, Wang and Borison [102, 104] demonstrated that several stimuli were detected by cells of the area postrema, termed the chemoreceptor trigger zone for emesis, which in turn activated the vomiting centre. Whilst there is no doubt that the area postrema when appropriately activated can induce emesis, its description as the chemoreceptor trigger zone has lead to the assumption that *all* chemicals in the circulation must induce emesis by this route.

The area postrema in man is a U-shaped structure a few millimetres long located in the caudal part of the fourth ventricle in the region of the obex [66]. Significantly, the area postrema is present in animals with (e.g. ferret) and without (e.g. rat) an emetic reflex, which suggests that it has functions other than emesis [25]. The area postrema is one of the circumventricular organs of the brain and is outside the blood–brain barrier and the cerebrospinal fluid–brain barrier [66]. It is therefore relatively permeable to polar molecules in the blood or cerebrospinal fluid, a feature which makes it ideally suited for a general chemoreceptor function.

Vestibular system. The vestibular labyrinthine system is essential for induction of emesis by motion stimuli. However, the evolutionary significance of an emetic response to motion is puzzling, but Treisman [98] proposed that when an animal is poisoned it may become unsteady on its feet and hence the labyrinths may be stimulated by such swaying motion. Obviously such a mechanism cannot apply to patients, although sudden movements of the head should be avoided after treatment to minimize any labyrinthine input to the vomiting centre, particularly in patients who have been relatively immobile for some time in a recumbent posture. The labyrinthine input should also be borne in mind when moving patients laying down on trolleys after surgery, as this additional input may induce emesis. Experimental studies in man suggest that the position of the head (and therefore the degree of labyrinthine stimulation) can influence the emetic response to apomorphine [53] which acts via the area postrema, and hence there is no reason why other emetic stimuli should not be affected in a similar way.

There is limited evidence that the vestibular system may be involved directly in the emetic response to some drugs. Studies in the dog revealed that removal of the vestibular system reduced the emetic response to lobeline, L-dopa and nicotine but not pilocarpine or apomorphine [71]. The most likely explanation is that these drugs are able to discharge vestibular afferents and to facilitate the primary effects they have on the emetic mechanism.

Higher influences. Studies in decerebrate animals have revealed that the integrative circuitry for the motor components of the emetic reflex reside in the brain stem and that such animals are capable of responding to emetic stimuli acting via the area postrema, vagus or even vestibular labyrinths. The role of higher cerebral influences is at present unclear but there is little doubt that inputs from such areas (e.g. limbic system) can induce nausea and vomiting [90].

These higher inputs appear to have a mainly facilitatory role in modulating the sensitivity of the brain stem emetic mechanism rather than acting as primary detectors of the emetic stimuli.

Miscellaneous inputs. Nausea and vomiting can be activated from several other regions of the body. Unpleasant tastes can induce nausea and retching, although it is not clear if this is a primary response or secondary to association with illness experienced as a result of prior exposure (a learned aversion). Nausea, and gagging in particular, can be evoked readily by mechanical stimulation of pharyngeal afferents projecting to the brain stem in the glossopharyngeal nerve. There may be a heightened awareness of this region associated with nausea.

After gastronomic over-indulgence, it was common practice for the Romans to retire to the Vomitorium and stimulate their tympanum with a feather to induce prompt emesis. This procedure stimulates the auricular branch of the vagus nerve, also known as Arnold's nerve or the Alderman's nerve.

Ventricular cardiac afferents may induce nausea and vomiting in man and experimental animals, and their activation probably accounts for these symptoms (particular nausea) before, or in association with, myocardial infarction [1, 92].

Organization of the vomiting reflex

The motor components of the reflex are mediated by both autonomic and somatic nerves. All these motor pathways have non-emetic functions. For example, the vagal non-adrenergic, non-cholinergic innervation of the stomach mediates gastric relaxation for the storage of food and the phrenic nerve contracts the diaphragm for inspiration. In the vomiting reflex, these and many other motor pathways are activated in a unique pattern. Vomiting can be considered to be a stereotyped motor programme involving co-ordination between many physiological systems and between the autonomic and somatic components of the nervous system. An impression of the degree of co-ordination may be gained from the observation that the retrograde giant contraction in the small intestine is not initiated until the proximal stomach has relaxed and retching does not start until the retrograde giant contraction has reached the stomach [61].

The term vomiting centre has been used widely to describe the central emetic co-ordinating mechanism. As in other areas of physiology, such terminology is now only used as a convenient shorthand for the co-ordinating system and as a substitute for an adequate description of the neuroanatomical substrates subserving such a function.

The co-ordination of the motor components of the vomiting reflex occurs in the brain stem. It is here that the vagal motor neurones supplying the gut and heart originate in the dorsal motor vagal nucleus and nucleus ambiguus. In addition, the dorsal and ventral respiratory groups regulating the phrenic nerve output from the cervical spinal cord are located in the brain stem as are the presympathetic neurones which maintain sympathetic tone to the heart and blood vessels. The output of these nuclei must be co-ordinated to produce the characteristic vomiting pattern described above. A promising candidate for this task is the nucleus tractus solitarius. This is probably the major integrative nucleus for visceral afferent information and, in addition, the ventral portion forms the dorsal respiratory neuronal group involved in the regulation of respiration [70]. Another candidate for the co-ordinating area is the parvicellular reticular formation and this has been reported to have many of the neuroanatomical connections consistent with such a role [69].

Motor components of the vomiting reflex

Whilst the often spectacular ejection of upper gastrointestinal contents is the most obvious component of the vomiting reflex, it represents only the culmination of a series of motor events involving both the autonomic and somatic divisions of the nervous system. For convenience we shall divide the reflex into two separate, but usually consecutive phases: pre-ejection and ejection.

Pre-ejection. The pre-ejection or prodromal phase is characterized by the sensation of nausea, the physiological basis of which is poorly understood. There are several visible signs such as cold sweating, cutaneous vasoconstriction and pupil dilatation mediated by sympathetic nerves and salivation mediated by parasympathetic nerves. In addition, changes occur in visceral function such as tachycardia and a reduction in gastric secretion, both mediated probably by sympathetic activation. Immediately before the onset of the ejection phase there is profound relaxation of the proximal stomach mediated by vagal efferent nerves activating post-ganglionic neurones in the stomach wall [48]. These neurones probably use vasoactive intestinal polypeptide (VIP) or nitric oxide as neurotransmitter. In conjunction with this, a retrograde giant contraction originates in the mid-small intestine and travels towards the stomach. The retrograde giant contraction is under vagal control and the transmitter involved is acetylcholine. These two gut motor events are of particular interest as they can be argued to have a clear function in the reflex—the gastric relaxation serving to confine orally ingested toxin to the stomach and the retrograde giant contraction returning any contaminated gastric contents to the stomach ready for ejection [39, 61]. The pre-ejection phase is usually, but not invariably, followed by the ejection phase.

Ejection phase. This phase comprises retching and vomiting with oral expulsion of gut contents only occurring during vomiting. The function of retching is unclear but it may be involved in overcoming the multicomponent antireflux barrier present in the region of the gastro-oesophageal junction (see [5] for discussion). Both retching and vomiting involve principally contractions of the somatic muscles of the abdomen and diaphragm. During retching the abdominal muscles and the entire diaphragm contract synchronously whereas during vomiting the peri-oesophageal diaphragm relaxes, presumably to facilitate passage of gastric contents into the oesophagus and hence to the outside world [7, 70]. Thus the actual expulsion of gastric contents is caused by compression of the stomach by the descending diaphragm and the contracting abdominal muscles under the influence of somatic motor neurones [7, 70]. During retching and vomiting, all animals adopt a characteristic posture, presumably to optimize compression of the stomach by the somatic muscles and to minimize strain on muscle groups and structures not involved in vomiting [7].

HOW ARE POSTOPERATIVE NAUSEA AND VOMITING TRIGGERED?

It is most likely that there is not one single feature of the surgical environment that is the single cause of PONV but the cause is probably multifactorial with a differing contribution from each factor depending upon the precise clinical situation. From the studies undertaken it is possible to identify the most likely triggers that induce PONV and to propose how they activate the reflex. For convenience each is reviewed separately. The factors are placed in the approximate temporal sequence in which the patient is exposed.

Preoperative Factors

Food

The induction of anaesthesia shortly after a meal is well known to be associated with emesis during both the induction and the postoperative period [22, 87]. In the case of elective surgery it is possible to be sure of the time the last meal was eaten but in the case of accident victims this may not be possible. In addition, although reasonable time may be allowed by the anaesthetist for gastric emptying to occur (4–6 h), this may still not ensure that the stomach is empty as there is large individual variation in normal gastric emptying rates with the liquid phase of a meal emptying exponentially and the solid phase linearly after a lag phase. Also, emptying rate is dependent upon the volume and chemical composition of the meal, with fatty meals being emptied relatively slowly. In addition, any trauma associated with the accident is likely to induce a slowing of emptying via sympathetic activation.

Although it may seem self-evident that the presence of food promotes retching and vomiting, the mechanism requires some consideration. Food, unless consumed in very large quantities, is not an emetic stimulus so why should it be so under these conditions? As mentioned above, postoperative emesis does not appear to be common in laboratory animals, however, emesis sometimes occurs on induction. In the ferret (a carnivore), urethane (ethyl carbamate) given i.p., produces a reliable, stable and long-lasting anaesthesia particularly suitable for neurophysiological studies. The time to surgical anaesthesia is about 10 min. In the vast majority of animals, when urethane is administered the animal rapidly becomes immobile, although there may be profuse salivation. However, if the animal has not been deprived of food for at least 12 h, retching and vomiting occur in almost all animals within a few minutes of administration [Bingham and Andrews, unpublished observations]. This emesis occurs after the animal has lost postural control but before surgical anaesthesia and hence may be considered to take place in stage II of anaesthesia (the excitement phase). Because of the nature of the anaesthetic and route of administration these observations do not have a direct parallel to the human experience, however they do illustrate an important point: two stimuli, neither of which alone induce emesis, can combine to induce the response. The food induces abdominal vagal afferent activation both by its volume and chemical composition and this in combination with a central effect of the anaesthetic may provide a sufficient emetic drive. In addition, in this phase where postural reflexes are lost, the animal may have nystagmus which provides an additional "pro-emetic" stimulus via a vestibulo–visual mismatch as occurs in motion sickness.

Following a meal, the gut also releases several hormones (e.g. gastrin, motilin, peptide YY), some of which have been shown to activate neurones in the area postrema when applied from micropipettes and to induce emesis when given systemically in high doses or into the cerebral ventricular system [29, 30, 31, 60]. Thus some circulating gut hormones could sensitize the area postrema and hence the emetic reflex to the effects of other stimuli. There is also an increase in hepatic portal vein 5-HT after a meal [86] or administration of the gastrin analog pentagastrin [46] and this may also have a sensitizing effect on the gastrointestinal afferents as has been suggested to occur after cytotoxic drugs and radiation and to contribute to the emetic side effects of these anticancer therapies [8].

In man, the problem of vomiting during the induction phase of anaesthesia can be minimized by using a rapid induction technique combined with cricoid pressure (Sellick's manoeuvre) as consciousness is lost [76].

The above discussion raises an important general issue that will be a recurrent theme in this review, of interactions between stimuli or sensitization to one stimulus by another. It also illustrates the difficulty of elucidating the mechanism of PONV as even the simple problem of the interaction between food and anaesthesia in the induction phase has several possible mechanisms.

The presence of food in the stomach is also reported to increase the incidence of nausea and vomiting in the postoperative period [22]. The mechanisms involved are probably similar to those outlined above but are augmented by the perioperative and postoperative factors outlined below.

Although we have concentrated on the pro-emetic effects of food, the nauseating effects of food deprivation should not be neglected as it is more common for patients to undergo surgery after a period of food deprivation. Palazzo and Strunin [75] reported a small study of healthy volunteers which showed that 56% of females reported nausea after fasting in the waking state for about 7 h whereas for men only 38% experienced nausea, beginning approximately 8.5 h after fasting. Whilst these studies may not be directly applicable to patients who are usually deprived of solids overnight before surgery in the morning, they may be relevant to patients whose surgery is delayed until later in the day.

Psychological stress

Patients are likely to be concerned about the forthcoming surgery and have some degree of stress response. The precise involvement of stress in the induction of emesis is poorly defined, although both animal and human studies have demonstrated that electrical stimulation of the cerebral cortex can induce emesis [90]. In addition, there are several endocrine responses to stress including the secretion of ACTH, growth hormone and prolactin. The possible involvement of these in PONV is discussed in more detail below as part of a consideration of the endocrine response to surgery.

Some studies have suggested that anxious patients may involuntarily swallow large amounts of air before operation and this may contribute to distension of the upper gastrointestinal tract that is thought to contribute to the genesis of PONV (see below). It has been suggested that aerophagy occurs in about 10% of cases [75].

The reason for surgery

The impact on PONV of the underlying problem requiring surgical intervention is often overlooked but may be a significant factor in some cases. In a patient in which nausea and vomiting are a component of the disorder for which they are requiring surgery (e.g. raised intracranial pressure, upper gastrointestinal tract obstruction) it is likely that the emetic system is already in a sensitized state. This argument may also apply to abortion performed during the early part of the first trimester of pregnancy when pregnancy sickness is present in the vast majority of women: one survey of 1000 women reported an 85% incidence of nausea and a 50% incidence of vomiting [9]. The mechanism responsible for pregnancy sickness is unknown but it is proposed that it represents a state in which the central emetic mechanism is sensitized. The influence of sex hormones on the emetic reflex is illustrated by the greater sensitivity of women to virtually all emetic stimuli (e.g. motion, cytotoxic chemotherapy) and the fourfold increase in risk of PONV after tubal ligation in the first eight menstrual days [16].

Perioperative Factors

Premedication

Differences in patient premedication is considered to be one of the main factors contributing to the large variation in the incidence of PONV between studies. Two major classes of premedicant agents are used: analgesics and antiemetics. The impact of current antiemetics upon the incidence of PONV is discussed elsewhere in this issue but it is worth mentioning that atropine in a commonly used dose of 0.6 mg i.m. can delay gastric emptying. This may contribute to postsurgical gastric stasis and hence PONV.

The main analgesics that have been studied in the context of PONV are morphine and pethidine. In considering the contribution of these and other drugs to PONV their intrinsic emetic and antiemetic effects which may be dose-related need to be considered together with the duration of action. The complexity of the problem can be illustrated by reference to animal studies of the emetic effects of morphine. In the ferret, the threshold dose of morphine-inducing emesis (retching or vomiting) is 0.1 mg kg^{-1} s.c. with all animals in the group responding at 0.2 mg kg^{-1} s.c. As the dose is increased, both the incidence and amount of emesis decrease until at 5 mg kg^{-1} there is no response to morphine, even though the animals do not show marked sedation [97]. Similar observations in the cat lead to the proposal of an opioid-activated antiemetic centre [34]. It is envisaged that the emetic effect of morphine and related opioids (e.g. loperamide) is via an action on opioid receptors (probably μ) known to be present in the area postrema (area postrema ablation abolishes the emetic response). As the dose of morphine is increased, it is envisaged that the antiemetic centre proposed to be located in the reticular formation is accessed and activated leading to a reduction in the emetic drive. This hypothesis is supported not only by the bell shaped dose–response curve seen with morphine, pethidine and loperamide, but also by studies demonstrating an antiemetic effect of high dose morphine and fentanyl against a range of other emetic stimuli including cytotoxic drugs [14]. The type of opioid receptor involved in the antiemetic component of the curve has not been identified with certainty and, although the μ receptor is strongly implicated from animal studies with fentanyl [14] and human studies with alfentanil [83], other studies using loperamide implicate the δ receptor [20]. Identification of the receptor type may lead to the identification of novel broad spectrum antiemetic drugs.

In contrast with the antiemetic effects of 5-HT_3 receptor antagonists against radiation and cytotoxic drug-induced emesis, these agents do not block morphine, morphine-6-glucuronide or loperamide-induced emesis in the ferret [20, 97]. In view of the differences in the metabolism of morphine between the ferret and man, caution should be exerted in extrapolating these results to man, although to date the ferret has been predictive of the clinical efficacy of this class of antagonist. The emetic effects of both morphine and morphine-6-glucuronide were blocked by naloxone.

The question of the relative contributions of morphine itself and its metabolites to the therapeutic and toxic effects has often been discussed. In man the major metabolites of morphine are morphine-3-glucuronide and morphine-6-glucuronide, the latter contributing about 10% of the metabolic product of morphine. Morphine-3-glucuronide does not appear to have any analgesic action or any significant binding to opioid receptors. Clinical trials of morphine-6-glucuronide show that it has potent analgesic activity ($0.15–0.6 \text{ mg kg}^{-1}$) but in contrast with morphine does not appear to induce nausea, dysphoria or clinically significant cardiorespiratory effects (see [97]). In general, it appears that the emetic and other side effects in man are caused by the actions of the parent molecule and not by one of the metabolites.

Three other actions of the opioids may contribute to PONV. First, morphine and pethidine in analgesic doses decrease gastric emptying. This leads to accumulation of gastric secretion and swallowed saliva, possibly contributing to distension of the stomach. As the effects of morphine on gastric emptying may be prolonged, this delay in emptying is likely to extend into the postoperative period when the patient may attempt to take liquids or even food. The decrease in gastric emptying is reported to be associated with an increase in antral and duodenal tone [74]. Thus, when the stomach is distended in this state, the tension in the muscular wall is higher than usual for a similar distension in the absence of morphine, leading to an increased discharge in the mechanoreceptive afferents which are known to be capable of triggering emesis when adequately stimulated.

Second, both morphine and pethidine appear to increase the sensitivity of the emetic reflex to activation by labyrinthine stimulation as indicated by the increase in the incidence of nausea and vomiting in ambulatory, as opposed to recumbent, patients given opioids [89]. The mechanism of this effect is not known but the opioids may have an action in the vestibular nucleus where leu-enkephalin-containing fibres and neurones are found (see [68]). This possibility appears unlikely because if the opioids directly activated the vestibular system, the incidence of emesis might be expected to be higher in recumbent subjects. An alternative possibility is that the activation of the area postrema and hence the vomiting centre by the opioids reduces the threshold for triggering emesis by other stimuli such as motion. This mechanism is supported by studies showing that the emetic threshold for apomorphine (acting on the area postrema) is dependent upon head position, presumably because of differing degress of labyrinthine stimulation [53].

Third, morphine and other opioids enhance the release of 5-HT from the small intestine, probably by disinhibition of tonically inhibitory neural pathways to the enterochromaffin cells [82]. The release of 5-HT has been implicated in the mechanism of emesis induced by anticancer therapies (see above). It appears that this mechanism does not play a major role in PONV, as 5-HT_3 receptor antagonists do not block emesis induced in animals by morphine, morphine-6-glucuronide or loperamide [20, 97].

An additional way in which opioids may influence emesis is via the release of vasopressin (ADH) from the posterior pituitary. Vasopressin is associated not only with nausea and vomiting but animal studies have shown that it may also reduce gut motility.

Intubation

At some point during the insertion of an airway via the mouth it is inevitable that there is stimulation of the pharyngeal mechanoreceptive afferents that project to the brain stem, predominantly in the glossopharyngeal nerve. Stimulation of these afferents can evoke the gagging reflex and, if stimulation continues, retching and even vomiting. The gag reflex may be triggered in anaesthetized animals (e.g. urethane anaesthetized ferret), although when the airway is in place, the gagging subsides. This is likely to be a result of combination of adaptation of the afferents and increasing depth of anaesthesia. The stimulation of irritant receptors in the larynx and upper airway is unlikely to contribute to the nausea and vomiting because, although these afferents can evoke the cough reflex, there is no evidence that they can trigger emesis.

Intraoperative Factors

The two main potential intraoperative contributors to PONV are the anaesthetic and the surgical procedure. The influence of these and their various components on PONV are discussed below.

Anaesthesia

As PONV is reported to occur with a wide variety of structurally diverse anaesthetic agents, we should consider whether the state of anaesthesia itself may contribute to the emesis in addition to any direct pharmacological effects of the anaesthetic agents.

How could the state of anaesthesia contribute to postoperative emesis? Although anaesthesia has been used to block emesis induced by radiation [106], and halothane itself has been reported to have some antiemetic effects at low concentrations [108], the state of anaesthesia may still contribute to PONV. During anaesthesia the patient may be in a recumbent posture and immobile for an extended period, particularly if muscle relaxants are used. In particular the head will be immobile leading to a reduction in the tonic discharge from the vestibular labyrinths for the duration of the surgery. Even during sleep the body never approaches such a state of immobility. When the patient begins to awaken from anaesthesia, the head is often one of the first parts to move, particularly if the patient tries to sit up, leading to a sudden vestibular discharge further enhanced if the patient is being returned to the ward in this drowsy state. In addition, there may be some nystagmus and the pupil diameter may not have returned to normal after anticholinergic premedication leading to vestibulo–visual mismatch or conflict as can be produced by some types of motion (e.g. swings, sea travel) [36].

Anaesthetics

General effects. If the state of anaesthesia itself was the main cause of PONV then the incidence of PONV may not be expected to be so variable and, in particular, there would be little difference between inhalation and i.v. anaesthetics. Therefore, it appears that it is the pharmacological and related properties of the anaesthetics themselves that make the main contribution. Although at first sight this appears self-evident because if anaesthetic agents are emetics then why does emesis occur primarily on induction and recovery and only rarely during anaesthesia when they are at their highest concentration? The answer presumably lies in the multiple effects of anaesthetics: emesis being induced by the anaesthetic agent but being blocked by the state of surgical anaesthesia. Thus, although the anaesthetic (emetic) is activating emetic pathways for the whole time it is present, the effects are only expressed outside the periods of surgical anaesthesia. Whilst this hypothesis provides a conceptual framework, it has not been formally tested and in fact some studies argue against such effects. For example, in man and the ferret, sub-anaesthetic concentrations of halothane can reduce emesis induced by either vagal afferent stimulation or other anaesthetics (trichloroethylene and nitrous oxide [108]). This antiemetic effect of halothane together with its rapid induction and recovery times may contribute to the low incidence of emesis with this agent. The potential antiemetic properties of other inhalation anaesthetics has not been studied, although such effects appear unlikely as cyclopropane, nitrous oxide and ether are associated with a higher incidence of emesis than halothane [33, 45]. In the urethane anaesthetized ferret, whilst emesis induced by apomorphine and cisplatinum is blocked, animals can still respond to abdominal vagal afferent stimulation, intragastric hypertonic solutions (e.g. NaCl) and occasionally radiation [6, 10, unpublished observations]. The apparent lack of relationship between the anaesthetic potency of the various agents and the emetic potency suggests that the mechanism of emesis resides in the pharmacological properties of the agents themselves.

Very few dose–response studies have been undertaken relating the incidence of vomiting and nausea to the dose of anaesthetic in the absence of surgery. One study [78] showed a general relationship between the percentage of nitrous oxide (20–40 %) and the incidence and intensity of nausea. With 40 % nitrous oxide the nausea persisted for several hours.

Pharmacological effects of the anaesthetics. The pharmacological action of the anaesthetics that has received most attention is their interaction with adrenergic receptors or their adrenomimetic effects. Jenkins and Lehay [54] proposed that agents such as cyclopropane and diethyl ether that are associated with a high incidence of PONV increase circulating concentrations of catecholamines whereas halothane and methoxyflurane that induce a lesser degree of PONV do not increase catecholamine concentrations and in fact have adrenergic receptor blocking properties. This hypothesis is supported by studies showing that emesis can be induced in the cat by intracerebroventricular injection of adrenergic receptor antagonists acting on the alpha-adrenergic receptor. Emesis was not induced by beta-adrenoreceptor activation. More recent studies have implicated both the alpha-1 and alpha-2 receptors in the area postrema in emesis [17]. As it is the circulating concentrations of catecholamines that are increased, the most likely source is the adrenal medulla reflecting an increase in sympathetic drive [91]. Emesis would then result from the effect of the catecholamines on the area postrema and neuronal recording studies in the dog have shown that both adrenaline and noradrenaline cause firing [29]. If this hypothesis is correct then alpha-adrenergic antagonists should block PONV but curiously this possibility appears never to have been tested directly, although the beta-adrenergic receptor antagonist propranolol has been of some benefit in cyclic vomiting in children [105]. The release of adrenaline by intense sympathetic activation of the adrenal medulla has also been implicated in the mechanism of emesis induced by hypotension and pain [75, 85].

The involvement of the area postrema in PONV has been tested in only one experimental study as far as the author is aware. Vomiting is seen in dogs and monkeys after cyclopropane [12]. In the dog, the incidence of emesis during recovery from cyclopropane anaesthesia (33.3 % in oxygen), administered 10–30 min after feeding, was related to the duration of anaesthesia: 5 min—35 %; 10 min—66.6 %; 15 min—80 %; 20 min—100 %. Ablation of the area postrema rendered the dogs refractory to the emetic effects of cyclopropane even when given at 3–6 times the emetic threshold. This study certainly implicates the area postrema in emesis induced by cyclopropane but does not allow a distinction to be made between a primary effect of the anaesthetic on the area postrema and a secondary effect via the release of an endogenous emetic such as adrenaline which then acts on the area postrema.

As noted above, recordings have been made from the area postrema and of necessity these studies have been performed on anaesthetized animals [2, 26, 29, 31] or isolated tissue [28]. In dogs anaesthetized with thiamyl sodium 25 mg kg^{-1} i.v. and pentobarbitone 25 mg kg^{-1} i.v., spontaneous neuronal activity was never recorded from the area postrema [29, 31]. In contrast, in rats anaesthetized with urethane and chloralose and cats anaesthetized with pentobarbitone, the area postrema was spontaneously active [2]. Area postrema neurones were also spontaneously active in explants maintained *in vitro* with a frequency range of 0.4–22 Hz [28]. From these limited studies it is not possible to draw any useful conclusions about the effects of anaesthetics on the area postrema, particularly as recordings have not been made in animals anaesthetized with the more emetic inhalation anaesthetics.

Although attention has focused on the effect of anaesthetics on the area postrema as the cause of emesis, an additional possibility could involve the antiemetic centre [34]. It is envisaged that this area of the brain stem when active inhibits the vomiting centre and thus prevents emesis. Anaesthetics have differential effects on neurones in different parts of the brain [11] and hence it is possible that PONV occurs because this centre is very sensitive to the depressant effect of the anaesthetic and is slow to recover its tonic activity in the postanaesthetic period. Thus PONV may result from both direct emetic effects of the anaesthetic and surgery and be facilitated by the indirect effect of prolonged inhibition of the antiemetic centre.

Recording studies of abdominal vagal afferents that are known to be capable of triggering emesis do not suggest that they are activated by anaesthetics such as urethane or barbiturates. If these afferents are involved in PONV, it is most likely by signalling the abnormal patterns of gastrointestinal motility associated with surgery and anaesthesia.

The above section has focused on the specific pharmacological effects of anaesthetics on the main inputs of the brain stem emetic co-ordinating mechanisms. However, anaesthetics have much more general pharmacological effects on the brain and PONV may be an expression of such effects rather than an indication of specific effects on the emetic reflex pathways. For example, there is considerable evidence from studies in rats that many anaesthetics (e.g. pentobarbitone, diethyl ether, halothane and nitrous oxide) influence 5-HT metabolism in the brain [3, 27, 41]. After halothane and nitrous oxide anaesthesia, there was a reduction in 5-HT synthesis and utilization, the former probably caused by reduction in tryptophan hydroxylase. These effects were apparent in both brain stem and forebrain tissue within 15 min of anaesthesia. Studies with diethyl ether in mice showed that it increased the synthesis of 5-HT whereas pentobarbitone reduced 5-HT turnover [3]. These studies illustrate that anaesthetics could trigger emesis by modulation of neurotransmitter release at forebrain sites known to be capable of activating emesis or at brain stem sites such as the nucleus tractus solitarius which receives inputs from the area postrema and the vagal afferents.

Physical effects of volatile anaesthetics. The incidence of PONV is greater with volatile than with i.v. anaesthetics and hence PONV could be contributed to by the physical effects of the anaesthetics. Although an increase in middle ear pressure has been implicated [39], the main effects are suggested to be on the gut [75, 76]. First, during manual ventilation with a mask (particularly by less experienced anaesthetists [51]) gas may pass into the stomach and upper intestines leading to distension and activation of abdominal, vagal and splanchnic afferents which in turn may trigger emesis. Palazzo and Strunin [76] considered that distension was a major factor and commented that emesis was less frequent if such ventilation was avoided by a period of preoxygenation [57]. Second, the gut may be distended by gas, particularly nitrous oxide. In the presence of an alveolar nitrous oxide concentration of 75% it has been estimated that the gut volume would increase by 500 ml h^{-1} of anaesthesia [see 56, 57]. In the stomach, such distending volumes are not likely to be of significance as the stomach has a considerable storage capacity but in the small intestine the impact is greater. It is worth bearing in mind that the belching reflex is likely to be suppressed under anaesthesia and in the postoperative period and hence this may lead to the prolonged accumulation of gas in the stomach that would normally be voided. In addition, as small and large intestinal motility are reduced the elimination of gastrointestinal gas as flatus is also reduced, leading to accumulation that may become painful.

Endocrine effects of anaesthetics. The endocrine effects of anaesthesia and surgery are extremely complex and their relative contributions to the observed changes have not been identified. A discussion of this extensive literature is beyond the scope of this review; however, a large number of peptide hormones (angiotensin II, AVP, bombesin, gastrin, insulin, neuropeptide Y, neurotensin, somatostatin, TRH and VIP) [29, 30] have been shown to induce emesis when given either i.v. or into the cerebral ventricles of animals, or both, usually at doses in excess of those required for the usual physiological actions. The mechanism for the induction of emesis is proposed to be via the area postrema and many (but not all) of these peptides can activate area postrema neurones when applied by pressure microinjection or iontophoresis.

Cardiovascular effects of anaesthetics. Arterial pressure frequently decreases during anaesthesia and this may be compounded further by haemorrhage and surgical manipulation. Hypotension may induce nausea and possibly vomiting, although the mechanism is unclear. One possibility is that hypotension may induce a large sympathetic discharge resulting in the release of adrenaline from the adrenal medulla which may then trigger emesis by an action on the area postrema. Another possible mechanism involves activation of vagal afferent mechanoreceptors with unmyelinated axons located in the ventricles of the heart. The precise physiological function of these afferents is unclear, but they can trigger emesis and may be responsible for the nausea and vomiting associated with vaso–vagal fainting, and infero–posterior myocardial infarct [92]. These receptors can be activated under several conditions, including myocardial ischaemia and tachycardia with hypovolaemia [92]. The latter could occur both during anaesthesia or in the postoperative period as the patient attempts to sit upright when there may be venous pooling in the lower body. These cardiac afferents also evoke reflex gastric relaxation predominantly via activation of vagal efferent non-adrenergic, non-cholinergic inhibitory neurones and this may contribute to the delay in gastric emptying associated with anaesthesia and surgery [1, 55].

Hypotension is generally considered to be more likely to be involved in the nausea and vomiting occurring during spinal anaesthesia. In a study of patients with spinal anaesthesia undergoing gynaecological surgery, the incidence of emesis was greater when systolic blood pressure was < 80 mm Hg. Maintenance of blood pressure using ephedrine reduced the incidence of emesis from 66% to 10% [85].

Gastrointestinal effects of anaesthetics. Anaesthetics may induce nausea and vomiting by causing disruption of gastrointestinal motility which may be compounded by the effects of surgery itself on gut function. Although anaesthetics modify motility throughout the gut, of particular relevance to emesis are the effects of anaesthetics on the lower oesophageal sphincter and gastric motility.

The effects of anaesthetics on the lower oesophageal sphincter (LOS) are important not because such effects may induce emesis but primarily because of the contribution that the LOS makes to preventing reflux of gastric contents into the oesophagus and hence regurgitation into the mouth with the associated risk of aspiration, particularly in recumbent subjects. In general, inhalation anaesthetics produce reduction in lower oesophageal sphincter pressure. This is seen with nitrous oxide in oxygen and is enhanced by the presence of halothane and enflurane [35]. A recent study showed a reduction in the number of spontaneous LOS contractions and the amplitude of provoked (balloon distension) LOS contractions with increasing concentrations of halothane (0.5–2.0 MAC). The authors argued that the mechanism of the reduction was not due to a peripheral effect of the anaesthetic but reflected a central action on the brain stem pathways regulating the vagal outflow to the LOS [42].

The general pattern of gastric motility that emerges from animal studies is one of a suppression of gastric and upper small intestinal motility by anaesthetic agents such as pentobarbitone, urethane, cyclopropane and halothane, although stimulation has been reported with ether that persisted beyond the period of anaesthesia [74] and a recent study of enflurane anaesthesia in the rat failed to demonstrate an effect on gastric emptying [15].

The mechanism of this suppression has been ascribed usually to a peripheral effect, for example, on the release of acetylcholine from the myenteric plexus or an increase in sympathetic discharge having either a direct effect or via the release of adrenaline. However, a recent study in the ferret suggests that a vagal mechanism may be involved. Gastric antral motility was monitored using implanted miniature strain gauges and the influence of pentobarbitone anaesthesia on the migrating motor complex (MMC) monitored [47]. The MMC occurs in the interdigestive phase (i.e. MMC activity is present in patients deprived of food before surgery) and is a periodic burst of motor activity that originates in the stomach and migrates along the small intestine to the terminal ileum. In man the periodicity of the MMC is about 90 min. In the ferret study, pentobarbitone abolished MMC cycling but activity began to return at the stage when the limb withdrawal reflex returned, although the animals were not capable of spontaneous movement. The effect of pentobarbitone on the MMC was not affected by naloxone or guanethidine but was modified by chronic abdominal vagotomy. This procedure prevented the abolition of the MMC by pentobarbitone but there was a reduction in amplitude. These studies indicate that the reduction in gastric motility under anaesthesia may be contributed to by vagal mechanisms, either a reduction in vagal cholinergic drive or an increase in the vagal non-adrenergic, non-cholinergic inhibitory pathways or a combination of both.

How can anaesthetics modify these vagal drives? One possible mechanism may be via the area postrema. Vagally mediated gastric relaxation may be induced by the action of emetic agents such as morphine and apomorphine on the area postrema [65] and a similar effect could account for both the emetic and motility suppressing effects of anaesthetics. It should be borne in mind that reduction in gastric motility almost invariably accompanies nausea and vomiting and thus the motility effects seen with anaesthetics may be a more general reflection of activation of emetic mechanisms rather than a specific effect of the anaesthetic on the autonomic nervous system. The same argument may apply to the sympathetic activation that accompanies anaesthesia as this occurs also in association with nausea and vomiting. The second possibility is a more selective effect of the anaesthetics on the vagal outflow from the brain stem by modulation of neurotransmission in the brain stem reflex pathways.

Although animal studies indicate that anaesthetics and anaesthesia alone can reduce gastric motility, for obvious reasons comparable information is not available for man, although it is likely that similar effects occur, particularly when combined with the effects of surgery (see below).

During anaesthesia and surgery, the reduction in gastric antral motility associated with relaxation of the pyloric sphincter may promote the reflux of bile into the stomach. Bile is known to be an irritant to the gastric mucosa and this may provide an additional stimulus to emesis by stimulation of gastric mucosal vagal afferents.

The general cardiovascular effects of anaesthesia were discussed briefly above but some anaesthetics may have more profound effects on the mesenteric circulation and reduce perfusion. The significance of this lies in the observation that relatively brief periods of ischaemia may sensitize the gut afferents to their natural stimuli. The mechanism probably involves the local release of agents such as 5-HT, substance P, bradykinin and prostaglandins. This means that in the postoperative period, as normal gut function returns, the central nervous system may be bombarded by an abnormal level of afferent activity from the gut adding further to the emetic drive from other factors.

An additional factor that should be considered is the effect of the anaesthetics on the release of 5-HT from the enterochromaffin cells in the mucosa of the upper intestine. The release of 5-HT from these cells has been implicated in the mechanism by which radiation and cytotoxic anticancer drugs induce emesis. The possible involvement of 5-HT is discussed elsewhere in this issue but 5-HT release can be induced by opioids, adrenaline, ischaemia and mechanical stimulation of the gut, factors that may be present during anaesthesia and surgery [82].

Effect of anaesthetics on intracranial pressure. Raised intracranial pressure may cause headache, nausea, vomiting and inhibition of gastric motility [44, 52]. Because of vasodilatory effects on cerebral blood vessels, halothane, enflurane, isoflurane and ketamine cause an increase in intracranial pressure that could contribute an additional trigger to emesis. Barbiturates (thiopentone, pentobarbitone) lower intracranial pressure and when used in combination with the above anaesthetics offset any tendency to increase in pressure [40].

General effects of the surgical procedure

The contribution of surgery itself to PONV can be resolved into two components; the general effects of virtually any type of surgical procedure and the effects of specific types of surgical procedures that are reported to be associated with a high incidence of PONV. The general systemic, endocrine and metabolic effects of surgery are familiar to anaesthetists and surgeons but which of the multitude of factors are most likely to be involved in PONV? These factors are examined briefly to illustrate this aspect.

Gastrointestinal motility. Although anaesthetics reduce motility, the effect of surgery is more profound and outlasts the duration of surgery. For abdominal surgery, the rank order of influence on motility appears to be skin incision < muscle division < laparotomy < gut manipulation [67]. Even in animals under full surgical anaesthesia, noxious levels of distension of the intestine sufficient to evoke reflex cardiovascular changes also produce a reflex, sympathetically mediated inhibition of gastric motility [73]. The inhibition of motility has non-sympathetic (vagal inhibitory or endocrine) components, as in experimental animals sympathectomy only reduces the duration of postoperative ileus but does not prevent it [67].

The significance of delayed gastric emptying and reduced intestinal motility induced by the anaesthetic and surgery is twofold. First, during surgery the delay or stasis leads to accumulation of fluid secretions, it may facilitate the reflux of bile into the stomach and may lead to the accumulation of gas (anaesthetic,. air swallowed before surgery or endogenously produced). All of these could induce activation of gastrointestinal visceral afferents including nociceptors if the stimulus is intense. Because the patient is anaesthetized and possibly paralysed, activation of these afferents does not induce emesis, but they induce several reflex endocrine changes, the effects of which may outlast the duration of surgery. As the patient gradually regains consciousness with these distensive stimuli still present, this afferent barrage may give rise to sensations of upper abdominal discomfort and nausea and even trigger vomiting. In addition, the prolonged stimulation of the afferents that occurs during surgery may serve to induce a long-lasting sensitization of the central nervous pathways involved in nociception and emesis. Second, the effects of the surgical trauma may persist long beyond the surgical period so that when the patient is conscious and apparently recovered from anaesthesia, gastric emptying and intestinal motility may still be reduced and hence the gut may be unable to cope with a normal meal even if the patient wishes to eat. This situation is analogous to patients with severely delayed gastric emptying who become nauseated or even vomit after a normal sized meal as occurs with non-ulcer dyspepsia.

Endocrine effects. The endocrine effects of anaesthesia and surgery are complex and the way in which they may relate to PONV have only recently begun to be investigated. Apart from adrenaline, one of the hormones with a relatively well described involvement in the response to surgery and emesis is vasopressin (AVP, ADH). This increases during surgery partly because of the effect of analgesia, but mainly because of the effects of surgery itself. Anaesthesia (halothane, isoflurane) appears to reduce the basal plasma concentration of vasopressin but it is increased markedly by the surgical procedure itself [57]. One study considered gastric manipulation to be the most potent procedure for the release of vasopressin and undertook an experimental study in the dog to identify the pathway [99]. They concluded that the main pathway was splanchnic nociceptive afferents with the vagal afferents not having any role. This contrasts with a study in the anaesthetized ferret in which electrical stimulation of the central end of the abdominal vagus was shown to be a potent stimulus for vasopressin release [50]. Whatever the pathway, there is no doubt that vasopressin is released during surgery in quantities that are many times those required for maximal antidiuretic activity. The reason why vasopressin is of such interest is that similar increases in plasma concentrations have been seen in man with other emetic stimuli such as motion, apomorphine and cytotoxic chemotherapy (see [7]). The increase in vasopressin bears a closer relationship with nausea than vomiting but it is as yet unclear if it is a cause or a consequence of the nausea, although some studies suggest that it increases before the onset of the reporting of nausea.

Specific effects of surgery

Certain types of surgical procedures are reported to be associated with a relatively high incidence of PONV and this section reviews the mechanisms that may be involved.

Ophthalmic surgery. Ocular surgery is associated particualrly with a high incidence of PONV in adults and children. A large study (607 patients) of patients aged 1 to > 60 yr provided a detailed characterization of the phenomenon [18]. Two types of emesis were identified: early, that occurring on the operating table at the end of surgery or soon after in the recovery ward and delayed emesis, occurring outside this immediate recovery period. The incidence of early emesis was higher with squint surgery (10 %) than with non-squint ocular (1.8 %) and orbital (2.7 %) surgery. For delayed emesis the incidences were 57 % for squint surgery, 18 % for non-squint ocular surgery and 23 % for orbital surgery. In contrast with a common perception that children are more sensitive to the emetic effects of ocular surgery, this study failed to identify an effect of age, although female gender was a predisposing factor for both squint and non-squint procedures. The time course of PONV was studied in children (mean age 7.2 yr) after strabismus surgery without any antiemetic administration [63]. Within 2 h of surgery 25 % were vomiting, by 4–6 h this had increased to 60 % and by 24 h had only increased slightly to 65 %. This pattern supports the conclusions from the above study that there are two components to the emetic response after this type of surgery.

It has been proposed that at least part of the PONV is caused by an oculo–emetic reflex triggered by manipulation of, and trauma to, the squint corrected eye [18]. The authors support this suggestion by pointing out that surgical procedures involving considerable intraoperative manipulation of the eye (retinal detachment surgery) and giving rise to residual eye discomfort are associated with increased incidence of early and delayed emesis whereas when there is little manipulation or residual discomfort low incidences of emesis occur. The afferent pathway of the reflex has not been investigated, however, the better known oculo–cardiac reflex provides some insight [43].

Pressure on the eyeball or traction of the extrinsic muscles of the eye evokes reflex bradycardia because of activation of vagal efferents and suppression of sympathetic efferents. The afferent pathway is in the trigeminal nerve that projects to the brain stem where the autonomic outflow to the heart can be influenced. It is likely that it is activation of these trigeminal afferents that triggers emesis, although this has not been demonstrated directly. Other mechanisms may be involved as emesis is uncommon in patients with trigeminal neuralgia when presumably there is intense activation of this pathway [52]. An additional mechanism that probably contributes to emesis when the operated eye is unbandaged, is the temporary interocular mismatch between the normal and corrected eye and the vestibulo–visual mismatch that this engenders. Both of these inputs may induce a motion-sickness-like state (see [36] for a review of the neurophysiology of motion sickness).

Ear, nose and throat surgery. The high incidence of emesis associated with surgery of the middle ear is perhaps not surprising and is likely to be caused by activation of the vestibular afferent pathways involved in motion sickness, particularly if the system has been sensitized by opioid premedication (see p. 9S). In addition to vestibular afferents, the auricular branch of the vagus (Arnold's nerve) supplying the tympanum may also be involved as stimulation readily induces emesis.

Nausea, gagging and emesis may be induced readily by mechanical stimulation of the pharynx resulting in activation of glossopharyngeal afferents projecting to the brain stem. The incidence of vomiting after paediatric tonsillectomy may approach 81% [101]. Surgical trauma may lead to some inflammation and sensitization of these afferents as occurs in patients with a "sore throat". Similar processes may be induced by the presence of an orotracheal tube and contribute to the emesis in the postoperative period even though the tube is removed. It has been reported that the incidence of PONV is greater in patients maintained with an orotracheal tube than with a nasotracheal tube [100]. This difference was ascribed to the angle at which the tubes impact the pharynx and presumably relates to different regional sensitivities for evoking the gag reflex from the pharynx.

The reason why nasal surgery should induce emesis is unclear as although stimulation of nasal afferents can evoke sneezing (involving some of the same somatic motor pathways as vomiting) and painful sensations, there are no reports of the direct induction of emesis. The emesis may be secondary to the pain but may also be caused by stimulation of pharyngeal and gastric afferents by swallowed blood and this may also be involved in ear and throat surgery.

Abdominal surgery. Intra-abdominal operations are more emetic than extra-abdominal operations irrespective of patient gender [75, 76]. During abdominal surgery it is inevitable that there is some displacement, manipulation and traction placed upon the gut and associated mesentery even if the gut itself is not the subject of the surgical procedure. The gut is invested with both vagal and splanchnic afferents that discharge in response to these types of mechanical stimuli [4, 49]: thus each surgical manoeuvre is signalled to the central nervous system. In addition to the gastrointestinal tract, other intra-abdominal and pelvic structures such as the kidney, bladder and uterus are invested with afferents that are activated by mechanical stimulation. It is the vagal afferents supplying the upper gut that have the main role in triggering emesis and, although a direct role for splanchnic afferents in activating emesis has not been possible to demonstrate, they clearly have a permissive role, which is discussed in more detail below [6].

In addition to direct activation of afferents, surgical manipulation of the intestine also induces release of 5-HT from the enterochromaffin cells. This 5-HT can cause both direct activation of the afferents and also produce long-lasting sensitization to other stimuli (see [7, 8]). Handling may also induce synthesis and release of a wide range of substances from the gut wall that may modulate visceral afferent activity (e.g. CCK, prostaglandin, interleukin) or enter the circulation to act on the area postrema (e.g. neuropeptide Y).

Gynaecological surgery. In response to virtually all emetic stimuli, women are more sensitive than men so it is perhaps not surprising that gynaecological surgery should be associated with a high incidence of PONV. Understanding the mechanism of PONV after gynaecological surgery is complicated by the prevailing hormonal status of the woman (e.g. four times higher incidence during menses and lower postmenopausally [16]). These observations are consistent with the view that the changing endocrine environment sensitizes the brain stem emetic mechanisms to the action of other emetic stimuli as has been proposed for pregnancy sickness [9]. One interesting observation is that the incidence of PONV was higher when dilatation was accompanied by curettage than with curettage alone [72]. This observation is also consistent with reports that vomiting is more common in gynaecological operations when the vagina is packed [77]. Studies in the rat have shown afferents supplying the uterus, the broad ligament and vaginal cervix that project to the spinal cord predominantly in the hypogastric nerve with a minor contribution from the pelvic nerve. These afferents are sensitive to gentle probing and rubbing in the region of the receptive field, ischaemic stimuli, bradykinin and 5-HT [19]. Limited evidence was presented that the afferents are more sensitive in oestrous and when the tissue was subjected to surgical manipulation. From these observations it is clear that the types of surgical procedures occurring during gynaecological surgery stimulate these afferents and, although there is no evidence that such afferents can directly induce emesis, they are likely to contribute to the general afferent load on the central nervous system which sensitizes the emetic pathways (see below).

In laparoscopic procedures, the insufflation of the abdominal cavity leads to abdominal discomfort if the abdomen is not adequately decompressed after the procedure, further adding to the general level of unpleasant sensations arising from the abdomen.

Time Course of PONV and the Role of Postoperative Factors

The factors described above may be involved in the postoperative period provided they have a sufficiently long time course or they have initiated secondary processes (e.g. sensitization of afferents) with prolonged effects. It is probable that both mechanisms are involved.

Typically, PONV lasts < 24 h with nausea and vomiting being most intense during the first 2 h, although the precise pattern depends upon many factors. In general retching and vomiting subside before the sensation of nausea.

Drugs and anaesthetics

Of the drugs given before operation, morphine and related opioids are the ones that are most likely to contribute to PONV by still being present in the postoperative period, having a direct emetic effect, sensitizing the vestibular system and by inhibiting gastric motility.

If anaesthetics have a direct pharmacological effect on the vomiting mechanism it might be expected that the agents most associated with PONV are eliminated more slowly, but the rate of elimination expressed as a percentage of initial alveolar concentration does not support this: nitrous oxide > cyclopropane > halothane > ether [84]. The lower incidence of emesis with halothane may be because it is present for several hours at sub-anaesthetic concentrations which are probably antiemetic [108].

The rate of recovery from anaesthesia also affects the incidence of PONV as sedation itself supresses the emetic reflex. Hence, if recovery is rapid, the patient may reach a state of arousal where emesis can be triggered before the emetic stimuli have subsided. In addition, when the patient becomes conscious he will be aware of his condition and able to perceive (and report!) nausea and pain. There may also be mismatched visual and vestibular inputs. In addition, the feeling of being "out of control" of the body, lightheaded and dizzy may make some patients anxious. The importance of giving reassurance to the patient in this period should not be underestimated. Removal of such inputs may go some way to explaining why long periods of postoperative sleep may reduce the incidence of PONV.

The use of neostigmine to facilitate the reversal of neuromuscular block has been associated with an increased incidence of PONV [59]. This could be a result of marked stimulation of gastric motility which would activate vagal afferents and trigger central emetic mechanisms sensitized by other factors. Direct activation of central cholinergic pathways may also be involved as pilocarpine and nicotine can induce emesis via the area postrema [24].

Prolonged disruption of gut function

After surgery, and especially general and abdominal surgery, there is a reduction in gut motility. Although gastric motor function usually returns before intestinal and colonic function, it is the disruption of gastric motility that leads usually to postoperative symptoms such as nausea and vomiting, particularly when the patient begins to eat. The delay in gastric emptying is caused by activation of inhibitory reflexes during surgery and their continued activation, probably as a result of activation of nociceptors resulting from tissue damage and trauma. The manipulation of the gut during surgery may have induced the release of local mediators (e.g. 5-HT) that induce sensitization of the gastrointestinal afferents. Under these conditions when the patient attempts to eat, food remains in the stomach adding its distensive effect to any fluid (saliva, gastric secretion, bile) that may have accumulated. One study in patients with severe PONV aspirated a volume of 698 ± 141 ml/24 h from the stomach [32]. In this sensitized state the afferent discharge induced may be capable of inducing emesis.

Although the activation of upper gastrointestinal tract afferents initially appears the most likely pathway for the induction of emesis in the immediate postoperative period, their significance is questionable. For the afferents to trigger emesis they must be active at least in the first postoperative hours when emesis is most frequent. As most patients do not attempt to take food or even appreciable volumes of fluid in this period, this cannot be the stimulus, nor can excessive motility, as motility is reported to be suppressed. If the visceral afferents are active then the most likely drive is from local mediators released by surgical manipulation but this occurs only during abdominal and pelvic surgery. Therefore, in non-abdominal surgery the role of the abdominal afferents in early PONV is probably minimal but may make a greater contribution when the patient begins to eat and drink before normal gastric function has returned.

Pain

The role of pain in the genesis of PONV is difficult to assess from a mechanistic viewpoint, although studies in man have claimed an association between the two. The problem with pain is that in animal studies the evidence for an involvement of splanchnic nociceptive afferents in emesis is limited. The major pathway for emesis is via vagal afferents with the splanchnic afferents having a permissive but not critical role. In addition, PONV is associated with surgical procedures in many areas that have never been implicated in direct activation of the emetic mechanism (e.g. uterus). How can these apparently discordant observations be reconciled?

In man there is evidence that pain is often associated with the sensation of nausea rather than with frank vomiting, with one study reporting that in the postoperative period only 10% of patients had pain without associated episodes of nausea in contrast to 58% in which the two were associated [75, 76]. It is well known that when subjects are nauseated they will be more likely to vomit, thus pain and vomiting may be linked via nausea. The pathway involved in nociceptor-induced nausea is not known, but activation of visceral nociceptors influences activity in the brain stem both in the nucleus tractus solitarius [13] and reticular formation [21, 79, 88]. From these areas the information may readily access regions of the cerebral cortex involved in conscious perception.

Pain itself induces general arousal or alerting of the central nervous system. It may be that by increasing the level of consciousness the patient is alert enough to experience the nausea generated by other inputs. Thus pain need not cause nausea but merely facilitate its expression.

Activation of nociceptors may also produce longer-lasting changes in the central nervous system that alter the threshold for emesis. In pathological pain (i.e. that following tissue damage) there is sensitization of the afferents at both peripheral and central sites [107]. The peripheral sensitization is caused by the release of a variety of agents (e.g. 5-HT, histamine, cytokines) from damaged and inflamed tissue. Central sensitization is caused by release of afferent neurotransmitters with a long duration of action and the release of excitatory amino acids that prolong synaptic potentials. More intriguingly, even brief periods of afferent activation may alter gene expression in central nervous system neurones resulting possibly in modification of many aspects of neuronal function [107]. If nociceptor activation produces similar changes in, for example, the nucleus tractus solitarius, this could provide a mechanism for pain reducing the threshold for induction of emesis from the conventional inputs (e.g. area postrema, gut afferents).

Activation of visceral nociceptor pathways inducing nausea appears to be an attractive mechanism to account for postoperative nausea associated with a variety of types of surgery. In addition, animal studies have demonstrated that visceral pain reflexes may be reduced by antagonism of 5-HT$_3$ receptors with some but not all antagonists [73]. Could such an effect be involved in the antiemetic effect of ondansetron in PONV? Unfortunately, this appears unlikely as when postoperative pain and anxiety were measured as part of a study of the effects of ondansetron in PONV after laparoscopic procedures, there was no effect on these variables even though PONV was reduced [23].

CONCLUSION

It is apparent from the above discussion that many factors associated with anaesthesia and surgery may contribute to induction of PONV. Although for almost all of these factors it is possible to provide a plausible, if not experimentally proven, mechanism by which they could influence the emetic reflex, for several our level of understanding is inadequate. In particular, little is known about the mechanism underlying the genesis of the sensation of nausea and the ways in which pain and nausea are linked. Another area of particular ignorance in understanding the overall mechanism of PONV is identification of the role of the anaesthetic. We have seen how some drugs such as alfentanil appear to have antiemetic properties ascribed to an agonist action at μ opioid receptors [83] depressing activation of the central emetic pathways but does a similar mechanism account for the effects of low concentrations of halothane or is it caused by an adrenergic receptor antagonist action as has been suggested? [108]. It has been proposed that the emetic potential of the anaesthetics relates to their ability to release catecholamines [54] but this has not been actively studied in recent times. Whilst considerable progress has been made in understanding the effects of anaesthetics on somatosensory systems [11], a comparable degree of knowledge is lacking for the brain stem regions involved in emesis such as the nucleus tractus solitarius and the area postrema. It is unclear if the emetic effects of various anaesthetics relate to anaesthetic action or to a side effect (e.g. opioid receptor activation), although a superficial comparison of the relative hydrophobicity—anaesthetic potency ranking and the emetic potency ranking—reveals little similarity indicating that the emesis is most likely a side effect or indirect effect of these agents and does not relate to their anaesthetic action.

The problem of PONV has some parallels in emesis induced by cytotoxic chemotherapeutic agents where drug structure, cytotoxic action and emetic effect are poorly related. However, as 5-HT$_3$ receptor antagonists are effective against emesis induced by a wide variety of cytotoxic drugs, but not other stimuli [6], it is argued that the emetic potential may be an index of their ability to release 5-HT from the gut mucosa [8]. Preliminary clinical data indicate that ondansetron, at doses comparable to those effective against radiation and cytotoxic drug-induced emesis, has some effect in PONV [58, 62, 64]. The vast majority of data has been gathered from female patients undergoing gynaecological procedures and, although the results are encouraging, they cannot be generalized to all forms of PONV. The main reason for this is that 5-HT$_3$ receptor antagonists are not general antiemetics: ondansetron does not affect motion-induced emesis in man [95] or emesis induced by intragastric irritants or morphine in animals [6, 20, 97]. Thus it is conceivable that, although 5-HT$_3$ receptor antagonists may be of benefit in abdominal procedures because they may release 5-HT and activate visceral afferent pathways or the area postrema in a similar way to that proposed for anticancer therapies, they may be ineffective in ENT or ocular surgery. However, if 5-HT$_3$ receptor antagonists are effective against nausea and vomiting after a variety of anaesthetic and surgical procedures then at last we may have the key to the mechanism of PONV.

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THE STUDY OF POSTOPERATIVE NAUSEA AND VOMITING

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Clinical investigators have been interested in factors related to postoperative nausea and vomiting (PONV) and in its assessment for several decades [10, 11, 13, 22]. It was reported as early as 1956 that the type of anaesthesia or operation, and also the administration of antiemetics was likely to influence the incidence and severity of PONV [8, 10, 22]. Recently it has become evident that among the many factors which are associated with PONV are included the experience of the anaesthetist [16] and the phase of the menstrual cycle [15]. As several factors may modify PONV and new drugs continue to be developed, it is important, therefore, that studies evaluating PONV are designed carefully. This review will present some studies on factors related to PONV and on the assessment of PONV. It is hoped that the methodology discussed may help investigators in designing and carrying out studies on PONV and may also help clinicians in reading the literature on PONV.

PATIENTS, PROCEDURES AND ANAESTHESIA

Several factors may influence PONV and these must be controlled when studying PONV.

Background factors

Table I lists some background factors which have been shown to influence the incidence and severity of PONV.

The frequency of PONV in children is the same in both boys and girls and is about twice that in adults [41] until it decreases after puberty [36]. PONV is more common in women than in men, a difference that is thought to be hormonal in origin [8]. Diamond, Bailey and McPhee [12] suggested that the effect of an antiemetic may be related to the gender of the patient. They suggested that there is a dose-dependent pharmacodynamic difference in the antiemetic action of metoclopramide, and that a dose of 50 mg in females is equivalent to 20 mg in males. A previous history of motion sickness and also emesis after previous anaesthetics, contribute to a higher incidence of PONV [20, 25]. It is obvious that administration of antiemetic drugs before surgery may decrease the incidence or severity of PONV [26, 27]. If women of childbearing age are studied, the phase of the menstrual cycle should be controlled [5, 15]. With advancing age, in excess of 70 yr, it appears that gender does not influence PONV [33].

Factors related to operation and anaesthesia

Table II lists some factors related to operation and administration of anaesthesia which have been shown to influence PONV. It is important that before conclusions are drawn from clinical data (e.g. on the efficacy of a new antiemetic drug) these surgical and anaesthesia related variables are controlled.

The incidence of PONV may differ in surface operations compared with intra-abdominal operations or ophthalmic surgery [22]. Surgery which involves stretching the gut wall may contribute to PONV whereas the presence of a nasogastric tube may decrease the frequency of symptoms [22, 38]. Premedication with opioids may stimulate the vomiting centre and cause nausea and vomiting [33], whereas premedication with atropine [33] and hyoscine [4] may prevent PONV. The incidence of PONV may depend on the anaesthetic induction agent used. Anaesthesia induced with etomidate has been associated with more PONV compared with thiopentone [29] and it has been suggested that propofol possesses antiemetic actions [24].

The incidence of PONV may be as great as 80% after ether anaesthesia [19, 22] whereas a low incidence of PONV has been noted after propofol

TABLE I. *Background factors which may modify PONV and which must be controlled in clinical studies*

- Patient age [36, 41] and sex [7, 12]
- History of motion sickness [20, 25]
- History of PONV after previous anaesthesia [20, 25]
- Administration of antiemetics before operation [26, 27]
- Phase of menstrual cycle [5, 15]

TABLE II. *Factors related to operation and anaesthesia which may modify PONV*

- Type and duration of operation [10, 12, 38]
- Type of premedication [4, 33]
- Type of induction agent [24, 41]
- Type of maintenance agent [19, 28]
- Reversal of muscle relaxation [21]
- Postoperative pain and its treatment [3, 32]
- Movement of patient [20, 31]

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KEY WORDS

Measurement techniques. Vomiting: nausea.

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anaesthesia [28]. One study [21] suggested that the incidence and severity of PONV were lower if neostigmine was omitted and muscle power allowed to recover spontaneously compared with patients who received neostigmine. It has been suggested also that postoperative pain may be a major cause of nausea [31, 32]. Movement of the patient from one bed to another or even transport to the ward may cause nausea and vomiting [20, 31].

ASSESSMENT OF NAUSEA AND VOMITING

Interpretation of symptoms

It is important to define precisely the meanings of nausea, retching and vomiting. Knapp and Beecher [22] gave excellent definitions 35 years ago of nausea and emesis, and these are still useful today. *Nausea* is a subjective sensation which should be evaluated by the patient, not by the observer. The feeling is best described as the desire to vomit without indulging in expulsive muscular movements. When nausea becomes severe, the secretion of saliva is increased and is associated with vasomotor disturbances and sweating. The feature that distinguishes *retching* from *vomiting* is production of even the smallest amount of stomach contents. When no stomach contents are expelled, the expulsive efforts are classified as retching. Retching is usually indicative of an empty stomach and is generally as unpleasant for the patient as vomiting. With both retching and vomiting, pharyngeal muscles relax, the soft palate is elevated, the diaphragm descends and there are spasmodic contractions of respiratory chest muscles and abdominal wall muscles. Retching and vomiting may also be grouped together under the common term "emetic episode".

Overall assessment of symptoms

It is necessary to define methods which categorize all symptoms over a defined period rather than listing the presence or absence of each of the symptoms. Knapp and Beecher [22] have termed nausea slight, moderate or severe and retching or vomiting slight if it occurred once or twice, moderate if there were three to five episodes and severe if it occurred more than five times in the first 4 h after operation. Bellville and co-workers [7] used a scoring system for nausea, retching and vomiting which provided a pooled numeric score for the 24-h period after operation and the overall score was then rated as none, mild, moderate or severe. Tigerstedt, Salmela and Aromaa [39] used a simple method where they rated nausea as none, mild or severe and vomiting as none, mild (one to two times) or severe (three or more times). Bailey and colleagues [4] defined nausea as mild if it lasted less than 2 h and severe if it lasted more than 2 h.

In several studies [15, 17, 25–27], we have evaluated PONV at five intervals during the first 24 h after operation: 0–2 h, 2–6 h, 6–12 h, 12–18 h and 18–24 h. At the end of each interval, a trained nurse assessed whether retching or vomiting had occurred and asked the patients if they felt nauseated. The results were scored as none, nausea, retching and vomiting. If the patients had all of the symptoms (nausea, retching and vomiting) they were categorized as having had vomiting.

If the postoperative period is not classified into several intervals it is still useful to separate the time spent in the postanaesthesia care unit from that spent in the ward. Bodner and White [9] used a subjective rating scale (from 0 = no nausea to 11 = as bad as possible) and a visual analogue scale (100 mm: no nausea to as bad as possible) for nausea. They also classified retching and vomiting together as emetic episodes and counted the total number of such episodes.

If an investigator does not want to study prevention of PONV but only treatment, it is necessary to define when treatment is given. In one study [9], the investigators waited until the patient had either nausea for as long as 10 min or at least two emetic episodes (i.e. retched or vomited at least twice) before antiemetic drugs were administered.

Rescue medication and outcome of PONV

The outcome which should be included in studies on PONV is the need to give an antiemetic or the need to give rescue medication if new drugs are being studied. The design of a study should define when to administer an antiemetic or rescue medication, that is to describe the criteria for administration of these drugs. For this purpose we have usually [15, 17, 25–27] used droperidol both as a definitive antiemetic and also the first rescue medication for prolonged nausea (lasting 10 min) or for vomiting. Bodner and White [9] used two rescue medications. The first one was administered for nausea lasting 30 min and the second for persistent nausea after failure of the first rescue medication to treat symptoms. The numbers of patients needing antiemetics or rescue antiemetics are good endpoints for statistical analysis.

Transient PONV is very distressing to the patient and every effort should be made by the anaesthetist to decrease this problem. Rarely, persistent nausea together with prolonged vomiting may lead to dehydration and interfere with nutrition and oral drug therapy. In day surgery, PONV may lead to delay in discharging patients home or unanticipated admission to hospital [23, 28, 40]. Thus in day surgery the assessment of home readiness and also the number of patients admitted to hospital after day surgery are important endpoints. However, studies using such endpoints would require very large numbers of patients. In inpatients, forceful vomiting has resulted in dehiscence of abdominal wounds and even rupture of the oesophagus [6]. These complications are as rare as aspiration of stomach contents into the lungs and it would not be possible to use these complications as outcome measures in studies of PONV.

Other adverse effects such as sedation, headache, facial flushing, constipation, visual disturbances and changes in biochemical variables obviously need to be studied with all new drugs. One example of the importance of including comparison of side effects is a recent study on the efficacy of ephedrine in the prevention of postoperative nausea and vomiting

TABLE III. *Factors involved in the design of a study of PONV*

Variables to be controlled are listed in tables I and II. These should not be different between groups.
Drugs should be administered in a double-blind, random fashion. If different patient groups/anaesthesias are used, stratified randomization may be required.
The main endpoint of efficacy should be patients with no PONV.
Nausea should be rated separately from retching and vomiting. Nausea may be rated as yes or no, as none, mild or severe, on a verbal (0–10 choices) or visual analogue (0–100 mm) scale.
Emetic episodes (i.e. retching and vomiting) may be assessed together as the number of emetic episodes or separately as retching and vomiting.
Adverse effects (sedation, headache) should be compared.
In day surgery, outcome variables, such as time to oral intake, time to discharge home and the number of unanticipated admissions to hospital are important secondary (or even primary) endpoints.
Non-parametric statistics should be used to compare different treatments and a large enough sample size should be studied before concluding that there is no difference between treatments.

[35]. In patients undergoing gynaecological laparoscopy, both ephedrine and droperidol were effective in preventing PONV compared with saline but patients given ephedrine were less sedated and could be discharged home earlier than patients given droperidol [35].

The study of PONV should take into account several factors including patient variables, type of surgery and anaesthesia, and should include assessment of the adverse effects of anaesthetic techniques or drugs studied. One example of the design of a study and of assessment of PONV is given in table III.

STATISTICS AND POWER CONSIDERATIONS

Because of the nature of the endpoints of efficacy obtained when assessing PONV, non-parametric statistics (e.g. Fisher's exact probability, chi-square or Kruskal–Wallis tests) should be used for comparison between different treatments. The main endpoint of efficacy should be the number of patients with no nausea, retching or vomiting. A second comparison may be the number of patients with nausea only. As discussed above, the severity of nausea and also the number of emetic episodes may also be secondary endpoints for comparison. However, it is recommended that the secondary endpoints are first well defined and after that comparisons are made between numbers of patients.

It is also of utmost importance that power analysis is applied in negative studies before concluding that there is no difference between two treatments in the prevention or treatment of PONV. An example of probably inadequate group sizes has been published recently [37]. The authors [37] concluded that nitrous oxide had no effect on PONV in patients undergoing day-case laparoscopy.

If the sample size is too small there is an increased risk of a false negative finding. What is the power of a test? The required size of a clinical trial is related to α (significance) and β (power) and the size of the difference between the success criteria of the two treatment groups [2, 30]. The power may be calculated retrospectively to assess the chance that a study had of detecting a significant and clinically relevant difference. The power may also be used prospectively to calculate a suitable sample size. An estimate of the incidence of, for example nausea and vomiting, should usually be available from previous studies or from pilot studies. For example, in two negative studies on PONV, Hovorka, Korttila and Erkola [16, 18] used power analysis to indicate they had an 80% chance of finding an effect (at $P < 0.05$) that stomach emptying decreased the incidence of PONV by 20% (from 70% to 50%) in 101 patients [16] and that nitrous oxide increased PONV by 20% in 150 patients (from 50% to 70%) [18]. Usually a power of 80–90% is recommended (80 to 90% chance of detection) and the significance should be at least < 0.05. Some authors [1, 30] have published graphs to estimate the sample size and power but accurate tables for sample size per group for a two-tailed test on proportions [14] have also proved useful [16, 18, 34] and are recommended.

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SURGICAL AND PATIENT FACTORS INVOLVED IN POSTOPERATIVE NAUSEA AND VOMITING

J. LERMAN

Seventy-five years ago, Flagg suggested that postoperative vomiting may result from causes other than anaesthetics: "there are at least three kinds of vomiting", the first of which he attributed to anaesthetics such as ether, the second to reflex responses, that is pain or ovarian surgery, and the last to opioids, for example morphine [30]. Before this report, anaesthetics alone were thought to be responsible for most postoperative nausea and vomiting (PONV). Subsequent investigations unfolded a spectrum of non-anaesthetic factors in the pathogenesis of PONV including age, gender, motion sickness, body habitus, surgical site and postoperative feeding procedures. This review summarizes our current understanding of the roles of two categories of non-anaesthetic factors, patient and surgical factors, in the pathogenesis of PONV.

Despite the recent advances in modern anaesthesia, only modest progress has been made in our understanding and treatment of PONV. Early studies reported incidences of PONV as high as 75–80% after opioid premedication and prolonged ether anaesthesia [4, 11, 13, 47, 83, 84]. In many of these reports, the patient population, premedication, anaesthetic and the surgical procedure were not controlled. In the second half of this century, however, these incidences have decreased by almost 50% for various reasons [7, 8, 16, 17, 24, 31, 45, 46, 59, 62, 70, 74, 80, 85]. Although the most common reason proffered for this dramatic reduction in PONV has been a change in anaesthetic practice from opioid premedication and deep ether anaesthesia to non-opioid or supplemented opioid premedication, lighter non-ether anaesthesia and barbiturates [34, 70], there have been no studies to support this hypothesis. Indeed the difficulty we have in explaining this reduction in the incidence of PONV in the past 30 years is symptomatic of the difficulty in understanding this entire area of the anaesthetic literature. It is evident that PONV is affected by many factors, including age and gender of the patient, premedication, anaesthetic technique and medication, postoperative analgesia and regional blocks, and type of surgery. The paucity of controlled, randomized, blinded studies makes it extremely difficult to establish the contribution of any of these factors, in whole or in part, to the incidence of PONV. In addition, there is lack of standardization of such basic issues as the period of observation in the post-anaesthetic period (ranging in some studies from 2 to 48 h) [7, 17, 22, 25, 34, 40, 53, 55, 57, 59, 72, 74] and the definition of nausea and vomiting [21, 34, 50]. As a consequence, the benefits of more sophisticated statistical analysis such as meta-analysis to identify causative factors in PONV has not been possible. More recently, investigators have undertaken scientifically rigorous studies under rigid and controlled conditions to identify the role of patient, surgical and anaesthetic factors in the incidence of PONV, thereby avoiding many of the problems of previous studies. It is my expectation that the contributions of patient and surgical factors to the incidence of PONV will be firmly established in the near future by the results of these rigorous scientific studies.

As the proportion of surgery has changed from inpatient to day-case surgery, the importance of factors associated with post-anaesthetic morbidity such as PONV has received increasing attention. The reason for this is a 1% incidence of unanticipated admission after day-case surgery [66]. Of the factors responsible for this admission rate, several merit consideration, including general anaesthesia, PONV, lower abdominal and urological surgery, anaesthetic and surgical time exceeding 1 h and age [33].

The incidences of PONV have remained fairly constant at 10% in the recovery room and 30% for the first 24 h after anaesthesia in several large series of patients for the past several decades. There may be several reasons for our lack of progress in reducing the incidence of this problem. The first is the vague definitions of PONV in the literature. Nausea remains a subjective complaint that requires patients to express their feelings. This complaint is difficult to elicit in children. In contrast, vomiting is an objective finding that ranges in severity from retching to protracted vomiting and may be quantitated in all age groups, including infants and children. In some studies, nausea, vomiting and

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TABLE I. *Patient and surgical factors affecting PONV*

Patient factors	Surgical factors
Age	Site of surgery
Body habitus	Adenotonsillectomy
Gender	Ocular
Delayed gastric emptying	Strabismus
	Gastric suction
Anaesthetic history	Mask ventilation
Motion sickness	Gynaecological
Anxiety	Duration of surgery
	Miscellaneous
	Postoperative fluids

retching were recorded whereas in others, only vomiting was recorded. These inconsistencies have limited the significance of interstudy analyses. The second reason is the non-rigorous nature of many of these studies on PONV. Many of the early studies on PONV were retrospective and there was no standardization of anaesthetic technique, patient population and surgical procedure; in some instances control groups and randomization of treatments were omitted. Because of these inconsistencies in study design, meta-analysis has been of limited value in clarifying the roles of these factors in PONV. The third reason was the relative low priority given to PONV as a postoperative complication. As PONV was not usually a life-threatening postoperative complication and because most patients were admitted to hospital for at least one night after surgery, there was little incentive to pursue this problem.

In the last two decades, however, there has been a renewed interest in the mechanisms of PONV, and pharmacological and non-pharmacological interventions that may reduce the incidence. Furthermore, recent studies have focused on manipulating only one variable at a time in controlled, blinded and randomized studies, thereby providing scientifically rigorous data on PONV. In addition, the rapid and dramatic shift from inpatient to day-case surgery in the past decade has resulted in a critical reappraisal of all postoperative complications, particularly those that delay discharge from the recovery room unit and those that lead to an unanticipated admission to hospital such as PONV.

This review examines two categories of factors that affect PONV: patient and surgical factors (table I).

PATIENT FACTORS

Age

The relationship between the incidence of PONV and age has been difficult to clarify from the literature, partly because of the effects of confounding uncontrolled variables such as premedication, gender, surgical case mix, anaesthetic technique and the duration of postoperative data collection. In spite of the effects of these confounding variables, there is evidence that the incidence of PONV changes with age: the incidence is least (5 %) in infants (< 12 months of age) [19], increases to 20 % in children less than 5 yr of age [19, 71, 86], to a maximum of 34–51 % in late childhood (6–16 yr of age) [19, 71, 72, 74, 80, 86] (fig. 1), remains constant or decreases slightly throughout adulthood (14–40 %) [8, 16, 17, 20, 24, 46, 68, 74, 80, 85] and into the eighth decade [8, 47, 59,74].

The incidence of PONV in adults is approximately 25 %, ranging between 5 % and 75 % [13, 17, 20, 21, 47, 68, 74]. The lowest incidence reported (5 %) reflects only those patients in whom PONV was greater than expected and required treatment [21]. A recent multicentre study reported incidences of PONV between 11 and 21 % for a wide range of surgical procedures and patients [20]. These probably reflect more accurately the current incidence of PONV in clinical practice.

The incidence of PONV in children varies between 9 and 38 % [19, 80]. Patel and Hannallah reported only a 9 % incidence in their 3-yr review which may represent a different case mix (ambulatory surgery that excluded tonsillectomies) [66]. Few studies have compared the incidences of PONV in children and adults under controlled conditions, (i.e. similar premedication, anaesthetics and surgery). Vance, Neill and Norris reported their experience with plastic surgery and found that the incidence of PONV in children (up to 12 yr of age) (38 %) was twice that in adults (17 %) [80]. The results of the latter study are consistent with those of a more recent very large review [19]. In the same study, the results were clear and uncomplicated as all children were unpremedicated and opioids were used sparingly. The greater incidence of PONV in children [19] compared with adults [21], however, must be interpreted with caution as the postoperative follow-up data were not collected prospectively for 24 h in all patients. Nevertheless, the infrequent use of premedication and opioids in their paediatric cohort suggested that PONV was caused by other factors, such as patient and surgical factors. These include characteristics unique to paediatric surgery (i.e. strabismus and tonsil surgery), anxiety, fear and pain [19]. Further studies are required to elucidate the importance of each of these factors in determining the incidence of PONV.

The small incidence of PONV in the infant age group may reflect an increased threshold for PONV, surgical factors such as the case mix, lack of effects of premedication or increased frequency of tracheal intubation [19, 71]. We have had a similar experience with the incidence of PONV in infants and children undergoing strabismus surgery [89].

Body habitus

Several reports have suggested that body habitus is an important determinant of the incidence of PONV, that is the incidence of PONV is greater in obese patients than in asthenic patients [4, 8, 74, 83]. However, these studies too were flawed by the presence of confounding variables. A possible relationship between PONV and body habitus was investigated in a well designed study of females undergoing first trimester abortion controlled for many of these variables [54]. Their results supported the existence of such a relationship. In spite of these studies, however, no relationship could be found between body mass index and the incidence of PONV in a recent large and carefully controlled trial

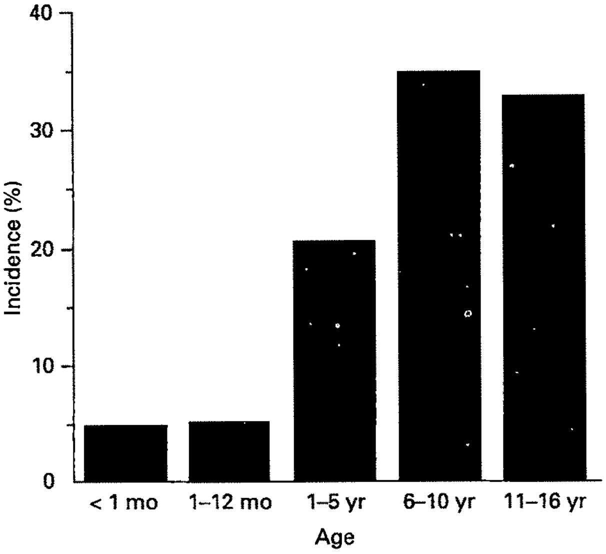

FIG. 1. Relationship between age and the incidence of PONV from infancy to adolescents after a wide range of types of surgery.

[59]. It is notable in the latter study that the lungs of these patients were not ventilated by mask before tracheal intubation. In fact, it is unclear if the relationship between body habitus and PONV reported in the above studies resulted from difficulties in anaesthetizing these patients (i.e. hypoxaemia, hypercapnia, hypotension or gastrointestinal distension leading to PONV) or obesity itself. On balance, at the present time there is insufficient evidence to conclude that a relationship between body mass index and PONV exists. Further studies are required to firmly establish a relationship between body habitus and PONV.

Gender

The incidence of PONV in adult females is approximately two to three times that in adult males [8, 17, 23, 29, 47, 59, 68, 74, 78, 90] and the severity of vomiting greater than that in males [68]. It has been suggested that this difference depends, in part, on the type of surgery: the incidence of PONV in females is similar to that in males after extra-abdominal surgery, but greater than that in males after abdominal surgery [27]. In surgery not normally associated with a high incidence of PONV, such as orthopaedic surgery, females have a high incidence of PONV (55% nausea and 40% vomiting) [48]. The greater incidence of PONV in females compared with males has been attributed to fluctuations in female sex hormone concentrations during the menstrual cycle [7, 74]. The greatest incidence of PONV in adult females occurs during the third and fourth week of the menstrual cycle [7]. Two recent retrospective studies explored the relationship between the incidence of PONV and the phase of the menstrual cycle. Both groups of women underwent gynaecological laparoscopy with similar anaesthetic techniques. In the first study [6], the overall incidence of PONV was 46%: the incidence was greater during the luteal phase (periodical data (Pd) 20–24, 77%) compared with that during the follicular (Pd 8–12, 32%) and pre- and menstrual phases (Pd 25–6, 18%). Nausea, retching and emesis were recorded during the 24 h after surgery. In the second study [38], the incidence of PONV was only 28%: the incidence was greater during the menstrual period (Pd 1–8, 51.6%) compared with that during the remainder of the menstrual cycle (21.6%). The discrepancy in results between these two studies may be attributed in part to the following: Beattie and colleagues reported PONV only during the first 2 h after surgery [6] whereas Honkavaara reported the incidence during the first 24 h [38]; and in both studies the serum concentrations of female sex hormones were not measured. If a relationship between PONV and the menstrual cycle exists, a prospective study in which PONV and female sex hormone concentrations are determined at the time of surgery is recommended.

The relationship is limited to adults as there appears to be no gender predilection for PONV in children less than 11 yr of age [7, 71, 74] or in the elderly in the eighth decade. This is consistent with similar concentrations of sex hormones in males and females in these age groups.

Delayed gastric emptying

The likelihood of PONV increases when gastric motility and emptying is retarded. Conditions associated with delayed gastric emptying include gastrointestinal obstruction, pyloric stenosis, collagen vascular disorders (i.e. scleroderma), endocrinopathies (i.e. diabetes mellitus), neuropathies, myopathies, ureamia, raised intracranial pressure and pregnancy [66]. Premedication with, for example opioids and barbiturates, given to allay preoperative anxiety, may also delay gastric emptying thereby predisposing to PONV.

History of PONV after anaesthesia or motion sickness

Several investigations have suggested that patients with a history of PONV after previous anaesthesia, or motion sickness, are more susceptible to PONV than those without a history [4, 17, 40, 44, 59, 68]. In one study, patients with a previous history of PONV experienced a three-fold greater incidence of PONV after a subsequent anaesthetic when the follow-up period was 24 h [68]. When the postoperative follow-up period was restricted to 6 h, a history of PONV did not correlate with an increased incidence of PONV [68, 70]. Susceptibility to motion sickness and adaptation to this phenomenon varies from individual to individual [76]. Further studies are required to clarify this relationship.

Anxiety

The importance of preoperative anxiety as a determinant of PONV has not been established. Preoperative anxiety is believed to delay gastric motility (and emptying) and increase gastric fluid volume, possibly via increased circulating stress hormones [61]. These hormones have been shown to induce emesis when instilled into the ventricles of cats [43]. Infants and children who are anxious often swallow large volumes of air and anaesthetic gases during induction of anaesthesia. In combination

TABLE II. *Surgical site as a determinant of PONV in adults [65] and children [71]. (*High incidence secondary to narcotic administration)*

Adults		Children	
Site	Incidence (%)	Site	Incidence (%)
Ovum retrieval	54	Cardiac catheterization	72*
Laparoscopy	35	Strabismus	76
Knee arthroscopy	22	Hernia, orchidopexy	54–58
Dental	16	Adenotonsillectomy	58
Dilatation and curettage	12	Plastic, penile, orthopaedics	37–49
		Removal of sutures	18

with the effect of nitrous oxide on the volume of gas within the gastrointestinal tract, this may contribute to the high incidence of PONV.

SURGICAL FACTORS

Site of Surgery

The relationship between the site of surgery and the incidence and severity of PONV is unclear. In two large studies, differences could not be detected in the incidence of PONV among a large variety of surgical sites [17, 47]. However, the difficulty of investigating such an effect is related to possible masking of a causal relationship by confounding variables (such as age, gender, premedication, anaesthetic and opioid administration). Nonetheless, there is increasing evidence that certain surgical sites may be associated with a greater frequency of, and in many instances, severity of PONV (table II): for example, intra-abdominal surgery (intestinal, gall bladder) has an incidence of 70 % compared with 15 % for abdominal wall surgery [13] with laparoscopic (gynaecological 40–77 %) [5, 40, 41, 55] and ear surgery (47 %) greater than head and neck surgery (25–33 %) [80], and the smallest incidences reported after dental, dilatation and curettage (not involving evacuation of the uterus) [26] and peripheral and superficial extremity surgery [13, 60, 65, 79].

In children, the surgical case mix differs from that in adults (table II). The surgical site associated with the greatest incidence of PONV in children is strabismus surgery. Hernia, orchidopexy and adenotonsillectomy are associated with the next most frequent incidence, and peripheral minor surgery the least likely to lead to PONV [71]. It is likely that more than one mechanism mediates the responses that culminate in PONV. PONV after intra-abdominal surgery may result from stimulation of autonomic afferents (i.e. vagal or sympathetic) from the intestinal wall or peritoneum or a resultant ileus and after adenotonsillectomy from irritant effects of blood on the gastrointestinal tract.

Adenotonsillectomy

The incidence of PONV after adenotonsillectomy in children is 36–76 % [35, 63, 69, 71, 87]. There are three causes for the high frequency of PONV after adenotonsillectomy: (1) irritant effect of blood on oesophagogastric chemoreceptors and nociceptors [15, 22, 75]; (2) irritation of trigeminal nerve afferents during surgery [15]; and (3) postoperative opioid administration. To minimize the effect of the first mechanism of PONV, direct oral suctioning is used during surgery to supplement cautery for haemostasis. Postoperative management includes positioning the child head down in the lateral decubitus position. The second and third mechanisms are difficult to control, although non-steroidal anti-inflammatory drugs may be effective.

Ocular surgery

Ophthalmological surgery is associated with a high incidence of PONV [1, 10, 36, 50, 81]. However, PONV does not uniformly affect all types of ophthalmological surgery: the incidence after intraocular and non-squint non-intraocular surgery is approximately 50 % that after strabismus surgery [9, 10]. This may be explained, in part, by the older age of the patients and the less stimulating nature of intraocular surgery (*vis a vis* the autonomic nervous system) compared with younger patients undergoing strabismus surgery [10]. The remainder of this discussion concentrates on strabismus surgery.

Strabismus surgery

Vomiting is the most frequent postoperative complication after strabismus surgery. The incidence of PONV ranges between 40 % and 88 % in children older than 2 yr of age [1, 9, 10, 14, 36, 39, 49–51, 81, 86, 88]. Age also affects the incidence of PONV after strabismus surgery (4–30 months, 28 %; 3–18 yr, 57 %) [86], although this is not supported by previous data [9]. PONV occurs rarely in the immediate post-anaesthetic period (i.e. the first 2 h after surgery) [72, 86]. In most instances, it begins after return to the ambulatory unit, during the journey home or at home 2–8 h after surgery. PONV may continue for up to 24 h after surgery.

Aetiology. The aetiology of vomiting after strabismus surgery is unclear. Several hypotheses have been proposed in an attempt to explain this phenomenon [9, 50, 81, 89]. These include traction on the extraocular muscles, distorted visual images, early ingestion of postoperative fluids and labyrinthine pathways. Manual traction on the extraocular muscles during surgery stimulates afferent neural pathways to the vomiting centre via the ciliary ganglion or labyrinthine pathway (oculogastric or oculo–emetic reflex). This resets the vomiting centre for emesis after emergence from anaesthesia. The second hypothesis invokes the effect of acute correction of the alignment of visual axes. The effect of a sudden change in axes might result in distortion of the visual images and PONV (optokinetic imbalance). To test this hypothesis, we covered the surgical eye in 60 children (who received no pharmacological prophylaxis for emesis) but found that this did not significantly decrease the incidence of PONV after strabismus surgery [Arellano and Lerman, unpublished data, 9]. The third hypothesis proposed to explain the incidence of PONV in these children is that of an emetic response to mandatory intake of clear fluids before discharge from hospital. Included in the discharge criteria for children after ambulatory surgery in most paediatric institutions at present is that the children ingest and tolerate clear fluids. Schreiner and co-workers reported that mandatory oral fluid intake after strabismus surgery was associated with a four-fold greater incidence of PONV in the ambulatory unit and a 50% prolongation of hospital stay compared with a group of children in whom fluid intake was elective [72]. Unfortunately, the authors did not provide data on the incidence of PONV *after* discharge from hospital for each of the two strabismus groups. In another study of fluid intake after surgery, parents were asked to withhold fluids 4–6 h or longer depending on the age of the child [86]. PONV was delayed until after discharge from hospital in 90% of those who vomited, although the incidence of PONV overall was similar to that reported previously (57%) [86]. However, the significance of the latter report is limited by the fact that parents were informed that early oral fluid intake may cause vomiting and that a control group was not included. The fourth hypothesis relates to the effects of changes in head position or motion on PONV. If sudden changes in head position or motion sickness initiates vestibular afferents to the vomiting centre, this could result in PONV [86]. Based on these studies, it would appear that traction on the extraocular muscles resets the vomiting centre such that emesis occurs after the first or second oral intake. Delaying the injection of clear fluids has no effect on the incidence of emesis, but clears the ambulatory unit and transfers the site of PONV from the day-case unit to home, or the journey to home.

Additional factors implicated in strabismus surgery. Several factors have been shown to increase the incidence of vomiting after strabismus surgery. Anterior displacement of the inferior oblique muscle is associated with a significantly greater incidence of PONV than is surgery involving other extraocular muscles [89]. This observation is consistent with the hypothesis that the probability of PONV increases as traction on the extraocular muscle increases. Thus less accessible muscles (such as the inferior oblique), are more likely to result in PONV after surgery.

Several other factors have been implicated in the high incidence of PONV after strabismus repair. Vomiting occurs more frequently after strabismus surgery in children > 3 yr of age than it does in infants and children < 3 yr of age [72, 86, 89]. Administration of oral fluids to children on recovery from strabismus surgery increases the incidence of postoperative vomiting compared with children who drink only when they request fluids [72, 86]. In a large retrospective study, repeat surgery was associated with an increase in the incidence of vomiting after strabismus surgery [89], although previous studies have not supported this finding.

Factors not responsible. Several studies have demonstrated that the incidence of postoperative emesis does not correlate with the number of extraocular muscles repaired [50, 75]. The incidence of vomiting was found to be independent of the following factors: type of ventilation (spontaneous compared with controlled ventilation), acupuncture (when applied after induction of anaesthesia) [88], i.v. lignocaine [18], covering the surgical eye (optokinetic effect), gender [89], opioids (codeine) [50, 89], duration of anaesthesia [89] and the surgeon [89].

Therapy. The type of surgery associated most often with PONV in paediatric anaesthesia is strabismus surgery. Although the morbidity after PONV and the risk of readmission after PONV are small, PONV is one of the most common causes of unanticipated hospital admission in the day-case paediatric surgical population [66, 67]. This is one cause of PONV that merits consideration for therapy, if not prophylaxis.

Abramowitz and co-workers first demonstrated that droperidol 0.075 mg kg^{-1} given i.v. at the end of surgery significantly decreased the incidence of PONV after strabismus surgery [1]. Subsequently, we demonstrated that droperidol 0.075 mg kg^{-1} decreased the incidence of PONV (24 h follow-up) from 60% to 25% [50]. This dose of droperidol, however, was associated with a 4–6 h recovery period. In an attempt to discharge children earlier, we investigated smaller doses of droperidol (0.025 and 0.050 mg kg^{-1}) [28]. These doses were not as effective in attenuating PONV as 0.075 mg kg^{-1} but more importantly, did not shorten the recovery period. Several other therapeutic interventions have been investigated recently. I.v. metoclopramide 0.15 and 0.25 mg kg^{-1} [14, 51], dixyrazine 0.25 mg kg^{-1} [49] and transdermal hyoscine [32, 39] have been used successfully in children to decrease the incidence of PONV after strabismus surgery and, in most instances, without extending the recovery period. I.v. lignocaine has had variable effect on the incidence of PONV after strabismus surgery in children [18, 81]. The effect of the new i.v. induction agent propofol, on the incidence of PONV has recently been reported [82]. Induction of anaesthesia with propofol 3.0 mg kg^{-1} i.v. and maintenance with propofol reduced the incidence of PONV after strabismus surgery by 50%.

Gastric suction

There are conflicting reports on the effectiveness of gastric suction in reducing the incidence, severity or both, of PONV [22, 23, 53, 74]. Gastric distention and an increased likelihood of PONV result from inadvertent inflation during manual ventilation of the lungs via a mask with or without gastric stasis after upper abdominal surgery. This may be attenuated by gastric suction [62]. On the other hand, Palazzo and Strunin [62] suggested that gastric suction would not attentuate opioid-induced PONV. The incidence of PONV in adult females is reportedly greater after their lungs are ventilated by inexperienced anaesthetists compared with more experienced anaesthetists [42]. Gastric suctioning has also been shown to be of no additional benefit when used to supplement an alfentanil anaesthetic in which droperidol was administered [37]. Several investigators recommend that if a gastric tube is used, it should be inserted after induction of anaesthesia and removed before emergence to minimize pharyngeal stimulation [62]. Early removal is suggested to preclude pharyngeal-induced PONV and has been proposed as a possible mechanism of gastric tube-induced vomiting. Recent evidence suggests that gastric evacuation may be particularly effective after laparoscopic gynaecological surgery [53]. However, a gastric tube that is curled or kinked in the stomach or passed into the duodenum may not only not prevent vomiting, but may stimulate retching and vomiting until it is withdrawn.

Mask ventilation

Manual ventilation by mask may result in gastric or intestinal inflation, or both. The mechanism by which mask ventilation causes PONV is likely a direct result of forcing gas into the gastrointestinal tract and distending the stomach and bowels. Experience of the anaesthetist may be an important determinant of the magnitude of the effect of mask ventilation on PONV [40]. Previous studies suggested that mask anaesthesia was associated with a greater incidence of PONV than anaesthesia in patients in whom the trachea was intubated [8, 22].

Gynaecological surgery

The incidence of PONV after gynaecological surgery depends on the type of surgery. Laparoscopy for diagnostic and therapeutic purposes is associated with a 36–60% (median value 50%) incidence of PONV [2, 5, 38, 41, 52, 57, 65]. Although the mechanism of PONV after laparoscopy is unclear, several investigators have apparently decreased the incidence of PONV to 13–33% by avoiding the use of nitrous oxide and fentanyl [2, 57,73]. Nitrous oxide may contribute to the incidence of PONV during laparoscopy by expanding intestinal and peritoneal gas (primarily carbon dioxide) volumes. Laparoscopy for ovum retrieval and therapeutic abortion (55%) [54, 65], major gynaecological surgery (58%) and hysterectomy (65–77%) [40, 55] are associated with a high incidence of PONV. In contrast, dilation and curettage does not usually cause a high incidence of PONV—incidence of 25–36% [34, 44, 56]. The mechanism of PONV after uterine and gynaecological surgery is unclear. Packing the uterus and pelvic pain have been implicated as possible mechanisms [64].

Other Factors

Duration of surgery

Bellville, Bross and Howland reported an almost three-fold greater incidence of PONV after surgery in parallel with an increase in the duration of surgery [8]. An increased incidence and severity of PONV has been associated with surgery of increasing duration by several investigators [12, 13, 17, 26, 27, 29, 71, 74]. In contrast, duration of surgery was not a significant factor in several studies [34, 47]. The possible relationship between duration of anaesthesia or surgery and the incidence of PONV is not easily explained. Increased effects of premedication, anaesthetics, including nitrous oxide, prolonged fasting and increased pain may contribute to the increased incidence of PONV in these patients.

Surgical position

The position of the patient during surgery has been implicated in the genesis of PONV. However, Gold found no effect in women undergoing gynaecological surgery [34]. The effect of this factor on the incidence of PONV has not been fully elucidated.

ENT surgery

The incidence of PONV after ear surgery ranges from 38 to 48% [69, 72, 80]. The type of ENT surgery that is often associated with PONV includes bat ear and middle ear surgery (cholesteatoma, tympanic membrane and ossicular surgery). There is little literature on the incidences of PONV with each of these types of surgery. Although not firmly established, PONV after bat ear surgery may be the result of reflex stimulation through the auriculo–temporal branch of the facial nerve [80]. In contrast, PONV after middle ear surgery may arise from increased middle ear pressure secondary to nitrous oxide or direct labyrinthine pathways [58, 77]. Further studies are required to clarify the extent of the PONV and its pathogenesis.

Pain

Andersen and Krohg noted that while abdominal surgery resulted in pain, the pain itself was associated with postoperative nausea. Paradoxically, the authors found that opioids did not increase the frequency of nausea, but actually relieved it [3]. It is my impression that in spite of this study, pain-induced nausea occurs infrequently, and that parental opioids are associated with more nausea and vomiting than they relieve.

Post-anaesthetic fluid intake

PONV has been observed to occur soon after the first fluid intake after emergence from anaesthesia [10]. This has been the subject of discussion for over 30 years [10, 17, 70]. Despite the apparent relationship between post-anaesthetic fluid intake and PONV, many institutions have standing orders that require that patients tolerate clear fluids before they are eligible for discharge from hospital, particularly after day-case surgery. Several authors have suggested that if fluids are withheld after strabismus surgery, adenotonsillectomy and ophthalmic surgery in children, then PONV may be delayed until after discharge from hospital, but even more importantly, the incidence of PONV may be reduced by 50% [72, 86]. In a recent study of postoperative fluid tolerance in children, fluid intake was offered electively only when the children were thirsty and hungry and they requested fluids. This resulted in a smaller incidence of PONV before discharge from hospital and earlier discharge from hospital but did not decrease the overall incidence of PONV [72, 86]. That is, many of the children vomited during transport home or at home within 24 h of surgery. The readmission rate for children who were discharged without having ingested fluids was small (0–0.06 %) and not a cause for concern [72, 86]. When a similar approach was applied to a study of children and adults who were recovering from ophthalmic surgery, the incidence of PONV after fluids were withheld for at least 4 h did not differ significantly from those who had fluids shortly after surgery [10]. However, the latter study may have been limited by too brief a period of postoperative fluid restriction. Nonetheless, if these preliminary data are substantiated by additional studies, oral fluids may no longer be a mandatory prerequisite for suitability of discharge from hospital and may facilitate earlier discharge from hospital. Whether withholding post-anaesthetic fluids attenuates the incidence of PONV remains to be established.

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POSTOPERATIVE NAUSEA AND VOMITING IN DAY-CASE SURGERY

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NAUSEA AND VOMITING

Nausea and emesis are the most common side effects in the postanaesthesia care unit (PACU). Contributory factors include opioid analgesic drugs, pain, the anaesthetic agent or technique, sudden movement or positional changes, a history of motion sickness, hypotension, obesity, the site of surgical operation, day of menstrual cycle and oestrogen level. Admission to hospital from a day-case unit may result not only from uncontrolled nausea and vomiting, but also from prolonged somnolence after treatment with potent antiemetics [59].

Opioid analgesics

Opioid analgesics are highly effective in both the prevention and treatment of postoperative pain. Controversy surrounds the use of opioid analgesics in the day-case patient because they may increase postoperative nausea and vomiting. The use of an opioid and nitrous oxide anaesthesia is associated with a greater incidence of nausea and vomiting than an i.v. or inhalation anaesthetic [65]. However, there are several studies which suggest that an opioid supplemented anaesthetic technique (fentanyl 1.5–2 $\mu g\ kg^{-1}$ i.v. or alfentanil 6–8 $\mu g\ kg^{-1}$ i.v.) results in earlier ambulation and discharge from the day-case unit [15, 21, 55, 64].

Pain

Andersen and Krohg established, in an inpatient population, a relationship between postoperative pain and the frequency of nausea in the early post-surgical period [2]. Complete pain relief without simultaneous relief of nausea was unusual. Patients who had inadequate pain relief and continued to have nausea after the first analgesic injection (50 % of the patients) were relieved of both complaints after a supplementary dose of an opioid. Only 10 % of patients complained of postoperative nausea without accompanying pain.

Jakobsson and colleagues noted that pain increases postoperative nausea and vomiting [22]. However, Parnass, McCarthy and Ivankovich, when evaluating the role of pain on postoperative nausea and vomiting in day-case patients undergoing arthroscopic knee procedures, found the incidence of postoperative nausea and vomiting was similar between patients with and without pain [45].

Anaesthetic agent and technique

Lonie and Harper noted a significant decrease in the incidence of postoperative nausea and vomiting in outpatients undergoing laparoscopic surgery when nitrous oxide was omitted from the anaesthetic regimen [34]. In female patients undergoing minor gynaecological procedures (dilatation and curettage, cone biopsy, and laser ablation of vulvar lesions), Melnick and Johnson found a decrease in nausea and vomiting when nitrous oxide was omitted from isoflurane and oxygen anaesthesia [38]. Recent studies on women undergoing laparoscopic surgery did not suggest that nitrous oxide was a prime causative factor in the incidence of postoperative nausea and vomiting [20, 53] (table I).

The mechanism of vomiting associated with nitrous oxide may be related to reduced middle ear pressure during recovery, stimulating the vestibular system by placing traction on the round window membrane [47]. Montgomery, Vaghadia and Blackstock studied this problem and found no association between postoperative reduction in middle ear pressure and postoperative vomiting in outpatient paediatric patients after nitrous oxide and halothane anaesthesia [42].

None of the studies that examined the relationship of nausea and vomiting after laparoscopy with the use of nitrous oxide considered the day of menstrual

TABLE I. *Nitrous oxide as a factor in nausea and vomiting. Percentage of patients experiencing nausea and vomiting who received or did not receive nitrous oxide (N_2O)*

	Patients with nausea and vomiting (%)	
Study	N_2O	No N_2O
Lonie and Harper [34]	29 %	4 %
Melnick and Johnson [38]	25 %	3.2 %
Sengupta and Plantevin [53]	51 % (nausea)	39 %
	18 % (vomiting)	10 %
Hovorka and colleagues [20]	34 %	32 %

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KEY WORDS

Surgery: day care. Vomiting: nausea.

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TABLE II. *Mean* (SD) *recovery room (RR) time and nausea and vomiting in patients undergoing different operations. Knee arthro. = knee arthroscopy; D & C = dilatation and curettage; Lap. = laparoscopy; Ovum = ovum retrieval. Significant difference* $P < 0.05$: **between patients with and with no nausea/vomiting; † between all operations; ‡ for incidence of nausea/vomiting between the different operations* [*44*]

	Operation				
	Dental ($n = 32$)	Knee arthro. ($n = 73$)	D&C ($n = 90$)	Lap. ($n = 175$)	Ovum ($n = 59$)
RR time (h)					
No nausea/vomiting	2.23 (0.50)	1.87 (0.53)*	1.66 (0.56)*	2.21 (0.90)*	2.73 (0.62)*
Nausea/vomiting	2.32 (0.55)	2.23 (0.63)	2.46 (0.86)	2.81 (0.63)	3.45 (0.85)
All patients†	2.24 (0.51)	1.94 (0.57)	1.77 (0.67)	2.41 (0.80)	3.10 (0.83)
Nausea/vomiting (%)‡	16	22	12	35	54
Nausea/vomiting per technique (%)					
No intraoperative opioid	12	17	11	30	52
Intraoperative opioid	33	37	17	42	60

cycle, but it has been suggested that emesis after laparoscopy may depend upon the phase of menstrual cycle [19]. The highest incidence of nausea, retching and vomiting was noted in patients who were in the luteal phase (day 20–24), whereas the lowest incidence was noted in patients who were considered in the pre- and menstrual phases (day 25–6). The need for antiemetics (droperidol) was greatest in the luteal phase. Lindblad and colleagues noted that the lowest incidence of emetic symptoms occurred on the 18th, 19th and 20th days with the greatest incidence occurring during the first 8 days of the menstrual cycle (greatest on day 5) [33].

The choice of anaesthetic induction agent is known to affect nausea and vomiting. Patients treated with ketamine have a significant increase in the incidence of nausea; there is at least a threefold increase in patients receiving etomidate compared with thiopentone or methohexitone and patients treated with propofol have a significantly lesser incidence of emetic symptoms compared with those treated with a barbiturate. Korttila and colleagues compared recovery after propofol for induction and maintenance of anaesthesia with thiopentone and isoflurane [27]. The propofol group tolerated oral fluids significantly earlier and experienced less emetic symptoms; none of the patients receiving propofol vomited in the PACU. For those patients who had emetic symptoms, the time in the PACU before being ready for discharge was significantly shorter for the propofol group compared with the thiopentone and isoflurane group. The severity of emetic symptoms, when they occurred, were significantly less with propofol compared with thiopentone and isoflurane.

Regional anaesthesia is an excellent choice for ambulatory surgery because of the low incidence of postoperative nausea and vomiting and earlier discharge of patients from the facility [43]. Extradural anaesthesia is administered to 50% of patients undergoing laparoscopy at the Virginia Mason Hospital (Seattle, Washington, U.S.A.); after surgery, nausea and vomiting were present in 38% of patients who had general anaesthesia but in only 4% of those who had received extradural anaesthesia [7].

Jensen and Wetchler found that ambulatory surgery patients who experienced emesis at some time in their postoperative recovery tended to be heavier than those who had no emetic symptoms [23]. Pataky and co-workers examined the incidence of postoperative nausea and vomiting after general anaesthesia for the five most common procedures in their day surgery unit [46]. Depending on the procedure, 12% to 54% of patients experienced emetic symptoms (table II). Nausea and vomiting prolonged PACU stay and increased the cost per patient [40].

TREATMENT OF NAUSEA AND VOMITING

Droperidol and metoclopramide

Cohen, Woods and Wyner observed limited efficacy of prophylactic low dose droperidol compared with metoclopramide in patients undergoing outpatient anaesthesia [12]. There was a lack of antiemetic effect for metoclopramide, but patients in the metoclopramide group were able to sit and walk, and were ready for discharge sooner than patients in the control or droperidol groups.

Rao and colleagues found that outpatient laparoscopy patients who received metoclopramide (10 mg alone or in combination with cimetidine 300 mg) had a significantly lower incidence of nausea and vomiting compared with the control or cimetidine-treated groups [50]. Patients had been instructed to fast from midnight and take their tablets with a small amount of water on the day of surgery just before leaving home. Rao and co-workers found that metoclopramide 10 mg i.v. relieved postoperative nausea and vomiting within 5 to 10 min and did not prolong duration of stay in the PACU. Williams and colleagues observed that low dose droperidol, metoclopramide or a combination of both, i.v. 15 to 30 min before induction of general anaesthesia was ineffective as an antiemetic in outpatients given alfentanil for laparoscopic procedures [62]. In contrast, Jorgensen and Coyle found that droperidol 0.02 mg kg^{-1} i.v. immediately after induction decreased the incidence of postoperative nausea and vomiting after alfentanil anaesthesia [24]. They did not find any increase in duration of stay in the PACU.

In comparing the effects of domperidone 20 mg, droperidol 2.5 mg, metoclopramide 10 mg or placebo, administered i.v. before induction of anaesthesia in 199 women undergoing gynaecological

TABLE III. *Frequency of nausea and vomiting in the postanaesthesia care unit in women undergoing outpatient laparoscopy under general anaesthesia who received combinations of metoclopramide (M), droperidol (D) and placebo (P). Percentage of 20 patients in each group. Chi-square tests were performed with raw numbers (percentage of total shown in table).* *$P < 0.05$ *compared with P+P group*

Groups	No nausea/vomiting (%)	Nausea only (%)	Nausea/vomiting (%)	Any nausea/vomiting (%)
M 5 mg+P	45	30	25	55
M 10 mg+P	55	25	20	45
P+D 5 μg kg^{-1}	60	20	20	40
P+D 10 μg kg^{-1}	75	20	5	25*
P+D 20 μg kg^{-1}	80	10	10	20*
P+P	35	25	40	65
M 10 mg+D 10 μg kg^{-1}	75	20	5	25*

ambulatory surgery, Madej and Simpson found that droperidol or metoclopramide significantly reduced the incidence of nausea and vomiting, whereas domperidone decreased only the incidence of postoperative nausea [36]. Wetchler, Collins and Jacob found that droperidol 0.625–1.25 mg, given i.v. immediately after tracheal intubation, was an effective antiemetic in outpatients undergoing laparoscopic tubal surgery [60]. Patients who received droperidol during anaesthesia had a lower incidence of nausea and vomiting in the PACU, a significant decrease in the severity of emetic symptoms and a shorter duration of stay than the control group.

Valanne and Korttila administered droperidol 0.014 mg kg^{-1} 5 min after induction of anaesthesia [58]. Droperidol caused less nausea (18%) or vomiting (7%) compared with patients given saline (27% and 11%, respectively).

Pandit and co-workers examined droperidol 5, 10 and 20 μg kg^{-1} i.v., metoclopramide 5 and 10 mg orally and a combination of the two drugs, in adult women undergoing outpatient laparoscopy under general anaesthesia [44] (table III). Oral metoclopramide alone had no effect on the incidence of nausea and vomiting. Droperidol 10 and 20 μg kg^{-1} and a combination of metoclopramide 10 mg and droperidol 10 μg kg^{-1} significantly decreased the incidence of nausea and vomiting in the PACU; however, only patients treated with droperidol 20 μg kg^{-1} required no additional antiemetic therapy in the PACU. Pandit and colleagues concluded that droperidol 20 μg kg^{-1} i.v. was the optimum effective antiemetic dose. Droperidol did not significantly increase the duration of stay in the PACU compared with the group that received only placebo. Poler and colleagues concluded that droperidol 20 μg kg^{-1} i.v. was an acceptable compromise between decreased emetic sequelae and excessive postoperative sedation [49]. Droperidol causes drowsiness and, if administered during the final phases of recovery care, may increase the duration of stay in the recovery room. The maximum antiemetic dose of droperidol should not exceed 2.5 mg for outpatients; as the dose is increased above 1.25 mg, drowsiness becomes more noticeable.

Melnick observed two cases of extrapyramidal reactions (restlessness, anxiety and acute dystonia) to low doses of droperidol (0.65 mg) [37]. Delayed side effects (anxiety, restlessness at home) were noted by 23.2% of women who had been given droperidol 1.25 mg during anaesthesia. Such symptoms were not noted in a control group. However, none of the symptoms was of sufficient severity to require treatment [39].

Caldwell, Rains and McKiterick reported a case in which a healthy woman developed symptoms of severe dysphoria, agitation and akathisia after administration of metoclopramide 10 mg i.v. before operation [11]. Side effects have been reported after administration of metoclopramide (drowsiness and lassitude are the most frequent, feelings of anxiety and agitation are usually mild and transient). Benztropine, a centrally acting anticholinergic at a dose of 2 mg i.m. followed after 15 min by 2 mg i.v. completely relieved patient symptoms. Although the benzodiazepines are used to treat akathisia, beta-blockers are considered to be more effective.

Transdermal hyoscine

The role of transdermal hyoscine has not been clearly defined in the prevention of nausea and vomiting. Pharmacokinetic studies have shown that the urinary excretion of hyoscine after application of a single patch is similar to that seen during continuous low dose i.v. infusion and that the drug continues to be absorbed for up to 3 days after initial application [54]. One would expect therefore that when administered by this route, hyoscine would provide prolonged protection, as in motion sickness. However, such data as exist do not support this hypothesis [3, 57].

Tigerstedt, Salmela and Aromaa concluded that transdermal hyoscine did not reduce the overall incidence of postoperative emetic sequelae, but that visual disturbances were more frequent when transdermal hyoscine was given [56]. However, Bailey and colleagues found that transdermal hyoscine was effective in reducing nausea, retching and vomiting in women anaesthetized for laparoscopy, although these problems still occurred in 37% of the women treated with transdermal hyoscine [4]. The patch was applied behind the ear on the night before surgery. Routine use of hyoscine as a transdermal preparation for prophylaxis in paediatric patients undergoing eye surgery is not recommended.

Gastric suctioning

For patients undergoing laparoscopic surgery, insertion of an orogastric tube (with removal of gastric contents) after induction of anaesthesia and tracheal intubation was found to result in a significantly lower incidence of postoperative vomiting compared with a control group [35], confirming the antiemetic efficacy of gastric suctioning [29].

Acupuncture

Dundee and co-workers noted that manual needling for 5 min at the P6 acupuncture point (Neiguan) resulted in a significant reduction in perioperative nausea and vomiting in 50 patients undergoing minor gynaecological procedures [13]. The application of low frequency (10-Hz) electric current for 5 min to an acupuncture needle placed at the P6 point was as effective as manual needling in reducing postoperative emetic sequelae [16]. The use of either transcutaneous electrical stimulation with conducting stud or pressure over the P6 point was found to produce a brief period (< 1 h) where nausea and vomiting were reduced but, after 1 h, the incidence of nausea and vomiting was the same as that for a control group [14]. In paediatric patients, acupuncture was not found to decrease vomiting after tonsillectomy and adenoidectomy [63] and P6 acupressure was not found to decrease vomiting after strabismus surgery [32].

Intraoperative fluid therapy

Intraoperative fluid therapy appeared to have no effect on the incidence of nausea and vomiting in the immediate postoperative period in paediatric patients compared with those who did not receive i.v. fluids [6]. The level of activity on the first day after operation was similar for both groups of patients. This contrasts with results in adult patients [25].

Neuromuscular block

A significant relationship has been found between postoperative emetic symptoms and antagonism of neuromuscular block with neostigmine in combination with atropine. The incidence of nausea and vomiting was significantly greater in patients when neuromuscular block was antagonized [26].

NAUSEA AND VOMITING IN CHILDREN

A significantly greater incidence of nausea and vomiting has been noted in paediatric patients who received opioid premedication for strabismus surgery; a significantly lesser incidence of vomiting was seen after anaesthetics lasting less than 30 min and in children younger than 3 yr [52]. Other studies have confirmed a significantly greater incidence of postoperative nausea and vomiting (up to 85%) in paediatric patients who undergo strabismus surgery [1, 18, 31]. After orchidopexy, up to 5% of patients may have to be admitted to hospital because of drowsiness, nausea and vomiting, or more extensive surgery than planned [10].

TABLE IV. *Vomiting after strabismus surgery in children (no prophylaxis).* * $P < 0.05$

Anaesthetic agents (induction/maintenance)	*n*	Postoperative vomiting (%)	
Propofol/propofol	9	11.0	22.2*
Propofol/halothane	9	33.3	
Thiopentone/halothane	10	50.0	58.8*
Halothane/halothane	7	71.4	

In several studies, droperidol 75 μg kg^{-1} has been found to be more effective in reducing vomiting after strabismus surgery than a dose of 50 μg kg^{-1} [1, 18]. When droperidol was given i.v. 30 min before termination of surgery, a dose of 75 μg kg^{-1} was associated with vomiting in 43% of patients compared with 85% in the control group. When droperidol 75 μg kg^{-1} was administered during induction of anaesthesia and before manipulation of the extraocular muscles, the incidence of vomiting was 10% compared with 47% in the control group [31]. Brown and colleagues recommended conservative management of children during and after strabismus surgery, involving gastric suctioning before tracheal extubation, replacement of preoperative fluid deficits, avoidance of opioids, and administration of a small dose of droperidol 20 μg kg^{-1} [9].

Hannallah and co-workers observed a significant decrease in emetic symptoms after strabismus surgery when propofol was used for induction and maintenance of anaesthesia (11%) compared with patients receiving an inhalation anaesthetic with halothane (71.4%) [17] (table IV).

Berry suggested that postoperative nausea and vomiting may be reduced in paediatric patients by restriction of oral fluids and limiting early ambulation [5]. I.v. fluids are given at a rate of 15–25 ml kg^{-1} h^{-1} for all operations lasting more than 15 min. Berry strongly believes that children should not be given liquids by mouth until they get home, and he discourages early ambulation.

Broadman and colleagues observed a decrease in the incidence of vomiting after strabismus surgery when patients were given metoclopramide 0.15 mg kg^{-1} i.v. immediately after entry into the postanaesthesia recovery room. The incidence of postoperative vomiting in a group given metoclopramide was 37% compared with 59% in the placebo-treated group ($P < 0.05$) [8].

5-HT$_3$ ANTAGONISTS IN POSTOPERATIVE NAUSEA AND VOMITING

Ondansetron, a 5-HT$_3$ selective serotonin antagonist, blocks receptors peripherally in the gastrointestinal tract and centrally in the medulla where the vomiting centre and chemoreceptor trigger zone are located. Ondansetron 8 mg i.v., given immediately before induction of anaesthesia, was found to be associated with decreased emetic symptoms after outpatient laparoscopy. In the PACU, 76% of the patients treated with ondansetron experienced no emetic symptoms compared with 58% given placebo ($P < 0.01$) [61]. In a multicentre study (580 ASA I and II female outpatients undergoing gynaecological surgery), those patients who received ondansetron 1, 4 or 8 mg i.v. immediately before induction of

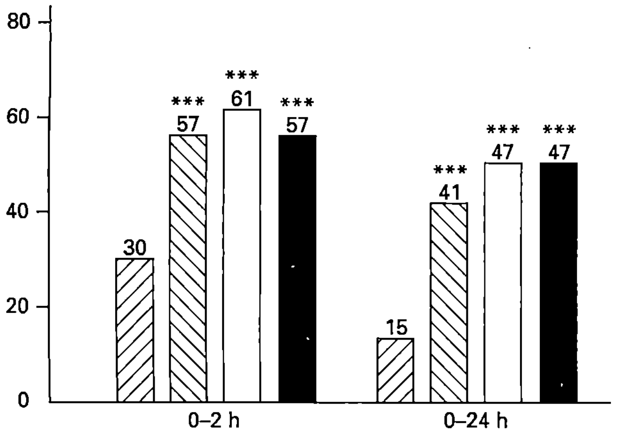

FIG. 1. Percentage of patients experiencing no return of emetic symptoms after receiving ondansetron 8 (■), 4 (□) or 1 mg (▧) i.v. or placebo (▨) in the postanaesthesia care unit during the first 2 h and first 24 h after operation. ***$P < 0.001$ compared with placebo.

anaesthesia had significantly less emesis than the placebo-treated group over the 24-h postoperative period. Ondansetron 4 mg i.v. was found to be the optimal prophylactic i.v. dose [28]. In patients experiencing emetic symptoms in the PACU, ondansetron 8 mg i.v. was an effective antiemetic in 78 % of patients compared with only 28 % of patients given placebo [30]. When patients who had nausea and vomiting in the PACU received ondansetron 1, 4 or 8 mg i.v. or placebo, the proportion of patients without emetic symptoms was significantly greater in those who received ondansetron 1, 4 and 8 mg during the 2 h in the PACU and for the first 24 h at home. There was no difference between groups for those patients receiving ondansetron [41] (fig. 1).

CONCLUSION

Droperidol 10 $\mu g\ kg^{-1}$ is the treatment of choice in the PACU at the Methodist Ambulatory SurgiCare (Peoria, Illinois, U.S.A.). For drowsy patients or those for whom droperidol is ineffective, metoclopramide 0.15 $mg\ kg^{-1}$ i.v. is administered. We treat with ephedrine 10–25 mg i.v. those patients who develop nausea on sitting up or when attempting to ambulate. The use of ephedrine prophylactically to decrease postoperative nausea and vomiting has both advantages and disadvantages. Rothenberg and co-workers found that administration of ephedrine 0.5 $mg\ kg^{-1}$ i.m. before termination of anaesthesia was as effective as droperidol 0.04 $mg\ kg^{-1}$ i.m. and significantly more effective than placebo in reducing postoperative nausea and vomiting [51]. In contrast, Poler and White found that ephedrine 25 mg i.m. before termination of surgery did not decrease emetic sequelae [48].

An important part of the pre-anaesthetic interview is identifying the patient susceptible to nausea. A history of motion sickness or emesis after previous anaesthetics should alert the anaesthetist to consider the use of antiemetics and gastric emptying (gastrokinetics or gastric suction), avoidance of nitrous oxide and opioids, and the use of regional anaesthesia. The patient susceptible to nausea should receive positive reassurance from all members of the staff to alleviate anxiety. The patient should be moved slowly at all times to avoid motion sickness. A warm blanket placed over such a patient may add to his or her sense of security. The patient should have limited pharyngeal suction at the conclusion of the operation in order to avoid stimulation of the gag reflex, and he/she should be allowed to wake up slowly in the PACU.

For the presence of intractable nausea and vomiting, the option of spending a night in hospital should be considered, but many patients prefer to recover at home. Patients should be instructed that if nausea and vomiting do not improve after rest at home, they should call their physician, or the emergency room if they feel it necessary to return to hospital and be admitted.

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ANAESTHETIC FACTORS CONTRIBUTING TO POSTOPERATIVE NAUSEA AND VOMITING

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This article reviews the anaesthetic contribution to postoperative nausea and vomiting (PONV). It does not discuss the physiology or mechanisms of causation of PONV, the patient and surgical factors contributing to, or the treatment of PONV, which are dealt with elsewhere in this supplement.

Review of the literature on anaesthetic factors contributing to PONV is rendered extremely difficult by lack of standardization of the definition of nausea and vomiting, and frequently by failure to standardize other factors which may contribute to this condition, including patient age, sex, type of operation, duration of anaesthesia, experience of the anaesthetist and postoperative management, including transport and mobilization of the patient. These problems are alluded to or dealt with in greater detail elsewhere in this supplement. The purpose of the present review is to describe briefly only those factors related to anaesthesia and for which there is reasonable evidence implicating them as causes of postoperative nausea and vomiting.

THE ANAESTHETIST

It has been known for many years that the experienced anaesthetist has fewer patients who suffer PONV than the inexperienced [5, 52]. Belville postulated that this may result partly from a tendency for the inexperienced anaesthetist to maintain deeper levels of anaesthesia [4]. More recently, it has been shown that manual ventilation of the lungs using a face mask before tracheal intubation was associated with more nausea and vomiting when it was performed by an inexperienced anaesthetist compared with an experienced one [31]; this effect persisted for up to 6 h after operation. The authors suggested that it may result from inadvertent distension of the stomach with anaesthetic gases. This mechanism would also provide an explanation for the excess PONV observed in obese patients, in whom ventilation of the lungs by face mask may be difficult [45, 61].

PREMEDICATION

Opioids

It is commonly observed that premedication with opioids results in an increased incidence of PONV. In 1960, Riding demonstrated that in women undergoing evacuation of retained products of conception, premedication with morphine 10 mg was associated with an incidence of PONV of 66.7% compared with 22.4% in controls. Atropine had significant antiemetic properties; a dose of 0.6 mg was associated with an incidence of PONV of 35.2% when given with morphine; when atropine was given without an opioid, the incidence was 11.5% [49].

Although attempts have been made in the past to compare the rates of PONV after different opioids, results from older studies should be treated with caution because of the less rigid methodology adopted at that time.

In 1957 Burtles and Peckett suggested that premedication with pethidine resulted in less PONV than that associated with morphine [8]. In contrast, Bellville, Bross and Howland [5] suggested the opposite. Furthermore, they demonstrated also that the extent of PONV was related to the dose of pethidine administered; the lowest incidence of emetic symptoms occurring with a dose of 1 mg kg^{-1} [5]. Dundee, Kirwan and Clarke demonstrated that a combination of morphine 10 mg with atropine 0.6 mg resulted in significantly more PONV in the 1–6-h period after operation than pethidine 50 mg with atropine 0.6 mg [19], which is perhaps not surprising in view of the fact that these doses were not equipotent. However, in a study comparing morphine 10 mg and atropine 0.6 mg with pethidine 100 mg and atropine 0.6 mg as premedication, before anaesthesia with propanadid for minor gynaecological surgery, Clarke and Dundee demonstrated that those receiving morphine had a greater degree of PONV in the first 6 h after operation [11]. They also found that morphine 10 mg resulted in the same incidence of PONV as diamorphine 5 mg, although increasing the dose to morphine 15 mg and diamorphine 7.5 mg resulted in a small increase in PONV in the diamorphine group [20]. As may be expected, in a subsequent study, the Belfast group

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also showed that the emetic effects of morphine and papaveretum were similar [39].

In paediatric practice, papaveretum has been shown consistently to be associated with high incidences of PONV [16, 51, 56]. Fentanyl is associated also with a high incidence of PONV in paediatric practice. In a recent study of the use of oral transmucosal fentanyl, the incidence of PONV was found to be 64% compared with 32% in children given placebo; when oral transmucosal fentanyl was administered with droperidol, the incidence was found to be 40% [24].

The use of opioids in a balanced anaesthetic technique as a substitute for volatile agents is associated with increased incidences of PONV. In a large multicentre study, Forrest and colleagues found that the use of fentanyl was associated with incidences of nausea and vomiting of 25.1% and 18.4%, respectively, compared with 18–19% and 11–13% for volatile anaesthetic agents [23].

The more recently introduced synthetic opioids are equally as culpable as the older agents in causing PONV. Large doses of sufentanil were found to be associated with increased PONV after outpatient gynaecological surgery [62], and alfentanil was found to be associated with a similar incidence of postoperative emesis as that induced by fentanyl [60].

Anticholinergic agents

The antiemetic properties of the old anticholinergic agents have been utilized traditionally as i.m. premedication. Clarke, Dundee and Love observed more than 25 years ago that hyoscine 0.4 mg was more effective than atropine 0.6 mg [12]. The antiemetic properties of the anticholinergic agent result from a central rather than a peripheral mode of action, as demonstrated by the fact that glycopyrronium, when used as an alternative to hyoscine, was associated with no antiemetic properties [43]; more recently, in a double-blind comparison of glycopyrronium and atropine in 100 patients, it was found that the former agent was associated with a two-fold higher incidence of PONV than that in the atropine group [53]. These results are consistent with the inability of the highly polarized glycopyrronium molecule to cross the blood–brain barrier.

Benzodiazepines

Although benzodiazepines are used in the management of chemotherapy-induced emesis, where it is thought they may possess antiemetic actions [1], there is no evidence to suggest that their use as premedication for anaesthesia is associated with antiemetic effects. Whilst Kamath and colleagues found that premedication with temazepam 10 mg or 20 mg was associated with a 22% incidence of PONV, compared with 36% in those who had received placebo, in a study of 182 women undergoing dilatation and curettage, variations in postoperative movement may have accounted for this difference [34]. In a large database of 3483 patients who had experienced nausea after general anaesthesia, Forrest, Beattie and Goldsmith found that the use of diazepam as premedication was not a risk factor [22], and similarly in children, Karlsson, Larsson and Nilsson observed no difference in the incidence of PONV between children premedicated with diazepam and those who received no premedication, although this was not a controlled study [35]. To date, there has been no well controlled prospective study which has examined the effect of benzodiazepine premedication on PONV.

ANAESTHETIC AGENTS

I.v. induction agents

It is well known that the i.v. induction agents are associated with differing degrees of PONV [10]. Thiopentone, used with nitrous oxide for minor gynaecological surgery, was found to be associated with a 12% incidence of PONV [55], whilst in a review in 1984, Clarke indicated that methohexitone, propanidid and etomidate were associated with significantly higher rates of PONV [10]. Although it is frequently assumed that ketamine causes postoperative emesis [59], there are no well controlled data to support this contention.

There is currently great interest in the lower incidences of PONV associated with propofol compared with thiopentone when used for i.v. induction of anaesthesia followed by inhalation agents [7, 18, 41]. The use of propofol by infusion for maintenance of anaesthesia was found, in a group at a high risk for PONV (children undergoing day-case strabismus surgery), to be associated with a lower incidence of PONV than in a group which received propofol for induction followed by maintenance of anaesthesia with inhalation agents [58].

Because of the low incidence of PONV associated with propofol anaesthesia, it has been postulated that this drug possesses antiemetic properties [41], but this has not been demonstrated conclusively [58].

Inhalation anaesthetic agents

Nitrous oxide. Cursory examination of the literature would suggest that the effect of nitrous oxide on the incidence of emesis is controversial. Unfortunately, many studies in this area are open to criticisms of inadequate size of populations, nonstandardized populations, lack of standardization of definition of emesis, invalid statistical assumptions, etc. Nonetheless, it is generally believed that nitrous oxide is associated with PONV, the possible mechanisms including actions on central opioid receptors, gut distension and pressure on the middle ear [42, 45].

There have been several studies on the effect of nitrous oxide on PONV in patients undergoing gynaecological laparoscopy. In a prospective, randomized study of 87 women, Lonie and Harper [40] found an incidence of emesis of 49% when nitrous oxide was used, but only 17% when it was omitted. In a similar study in 80 patients, Sengupta and Plantevin [54] found an incidence of vomiting of 33% in the group which received nitrous oxide, but only 12.9% in the control group. Whilst there was no significant difference between the two groups, a power analysis had not been performed and it is likely that the number of patients examined was too small to provide a statistically significant result. When a study of 185 women undergoing laparoscopic sterilization was performed, Felts, Poler and Spitznagel found that the overall incidence of nausea in the nitrous oxide–enflurane group was 29.2%, and 9.3% in a group receiving air–enflurane; there was a highly significant difference in these incidences [21]. However, Hovorka, Kortilla and Erkola found no difference between those receiving nitrous oxide or those receiving air in a study of 150 women undergoing gynaecological laparoscopy [29].

The role of nitrous oxide as an emetic stimulus during major surgery is more difficult to define. Nitrous oxide was not shown to be associated with excessive emesis in a group of 110 women undergoing elective abdominal hysterectomy [37]. Similarly, in a large randomized study of 780 patients undergoing various procedures, Muir and colleagues found no association between the use of nitrous oxide and subsequent PONV [44].

Ranta, Nuutinen and Laitinen studied the effect of nitrous oxide on PONV after upper abdominal surgery in 50 patients, and found no difference in the incidence of nausea [46]. They suggested that any beneficial effect provided by omission of nitrous oxide demonstrable in minor surgery may be masked by stronger factors provoking nausea after major surgery.

In support of this hypothesis is the recent demonstration in a study from our department that children undergoing myringotomy under nitrous oxide–oxygen–halothane anaesthesia had a significantly higher incidence of postoperative vomiting than a control group of children anaesthetized with oxygen–halothane [Wilson, personal communication].

Volatile anaesthetic agents

The old, long-established anaesthetic agents which are no longer in clinical use, such as ether and cyclopropane, were associated with a very high incidence of postoperative nausea and vomiting [27, 45]. It was suggested that vomiting was more frequent with those anaesthetic agents that increased circulating concentrations of catecholamines (e.g. ether, cyclopropane and trichlorethylene) [33]. Methoxyflurane was suggested as having lower emetic sequelae than halothane [26].

The volatile anaesthetic agents in current use, notably isoflurane, enflurane and halothane, are known to be associated with lower incidences of PONV than balanced anaesthesia using opioid agents. Whilst there may be differences in emetic sequelae caused by each of these three agents, such differences are small. Some of the older studies in relatively small numbers of patients suggested that there were differences between the three agents, for example Tracey, Holland and Unger compared halothane, enflurane and isoflurane in 75 women undergoing minor gynaecological surgery, and although there were no differences in the recovery room, 32% of patients who had received isoflurane had nausea on the first day after operation compared with 8% and 12% for halothane and enflurane, respectively [57]. In a study of 180 patients undergoing abdominal hysterectomy, Hovorka, Kortilla and Erkola [28] found that patients who had received isoflurane had less emetic sequelae (27%) in the first 2 h after operation than those who had received enflurane (45%). In contrast, in the large multicentre study of 17201 patients undertaken by Forrest and colleagues [23], retrospective analysis of data revealed a similar incidence of emetic symptoms for halothane, enflurane and isoflurane (nausea 18.3%, 18.5% and 19.1%; vomiting 12.6%, 11.9% and 11.5%, respectively). In both of these last cited studies, the substitution of fentanyl for any of the volatile agents used resulted in a considerable increase in PONV.

It was suggested in 1963 that halothane may possess antiemetic properties in subanaesthetic concentrations [25] but there are no recent data to confirm this suggestion; none of the data from studies in which anaesthetic concentrations have been used provide confirmatory evidence for this hypothesis.

Neuromuscular blocking agents

Neuromuscular blocking agents *per se* are not thought to have effects on PONV [45], although antagonism of residual neuromuscular block with a mixture of neostigmine and atropine does result in increased emesis, despite the antiemetic action of atropine. This suggests that neostigmine has significant emetic properties [36].

ANAESTHETIC TECHNIQUES

Spinal anaesthesia

It is generally assumed that spinal anaesthesia alone is associated with a lower incidence of PONV than general anaesthesia, as it avoids the emetic effects of opioids and volatile anaesthetic agents. We have been unable to find a prospective comparison between the incidence of PONV after spinal and general anaesthesia using the appropriate methods described by Korttila in this supplement. There is a quoted paper which purports to describe a difference between general, extradural and spinal anaesthesia [48], however those who quote this work frequently fail to indicate a significant difference in opioid administration, making interpretation difficult. The reported incidences of PONV after spinal anaesthesia suggest that the assumption is probably correct, provided that complications associated with spinal anaesthesia, such as hypotension and high block, are avoided.

The reported overall incidence of PONV after spinal anaesthesia in the older literature varies between 13% and 42% [3, 14, 47]. In a recent prospective study of 952 patients undergoing spinal anaesthesia, Carpenter and colleagues [9] reported nausea in 18% and vomiting in 7% of patients. They found that there was a greater incidence of nausea in patients who were given local anaesthesia with phenylephrine or adrenaline than in those given plain local anaesthetic (the risk increased 4.6 and 3.9 times, respectively). Use of procaine was associated with the highest incidence of PONV in comparison with other local anaesthetic solutions. The following factors were found to be associated with postoperative nausea.

Height of the block. Patients in whom the block height was > T5 had a 3.9-fold increased incidence compared with those with lower blocks.

Resting heart rate. In patients in whom the resting heart rate before induction of local anaesthesia was > 60 beat min^{-1}, the incidence of nausea was increased 2.3-fold compared with those patients with resting heart rates of less than 60 beat min^{-1}. This may reflect preoperative anxiety which has been suggested as a patient factor influencing the incidence of PONV [38].

Hypotension. The incidence of nausea in patients who have developed hypotension was increased 1.7 times compared with those in whom hypotension did not occur.

Local anaesthetic used. The use of procaine and the addition of either phenylephrine or adrenaline were associated with an increased incidence of nausea.

This study confirmed an early observation by Crocker and Vandam who retrospectively analysed the records of spinal anaesthetics administered between 1956 and 1957 [14]. They found that operative emesis was associated with: pain appreciated during surgery; hypotension, as defined by either systolic arterial pressure < 80 mm Hg or a decrease of > 40 mm Hg; a block extending to or above the T4 dermatome; and the concomitant use of intrathecal adrenaline. However, Crocker and Vandam [14] ascribed this factor to the presence of a higher level of block or the type of block produced rather than adrenaline itself.

Both this study and that performed subsequently by Ratra, Badola and Bhargava [47] examined the incidence of intraoperative but not postoperative emesis. Ratra, Badola and Bhargava also found that intraoperative hypotension, as defined by systolic arterial pressure < 80 mm Hg, was associated with an increased incidence of vomiting and retching and that administration of 100% oxygen to patients during spinal anaesthesia ameliorated this problem.

As might be anticipated from the foregoing, it has been observed that prevention of hypotension during spinal anaesthesia by the administration of ephedrine is associated with a reduction in the incidence of intraoperative nausea and vomiting [15].

Regional anaesthesia

Avoidance of general anaesthesia or spinal anaesthesia reduces the incidence of intraoperative and postoperative emesis. In a prospective study of retching and vomiting (but not nausea), Dent, Ramachandra and Stephen found an incidence of emetic sequelae of 11.1% after spinal anaesthesia compared with 4.3% after peripheral regional anaesthesia [17]. Similarly, in a prospective study of both nausea and vomiting over 24 h after surgery, Bonica and colleagues observed an incidence of emesis in 21.1% of patients after spinal anaesthesia but only 8.8% after local block of limbs [6].

INTRAGASTRIC TUBES

There have been several investigations of the effect of passing orogastric and nasogastric tubes during operation on the incidence of PONV. However, the results are conflicting. In some older studies, Dent, Ramachandra and Stephen [17] found no benefit of stomach decompression by means of a gastric tube but her study groups were not matched. In contrast, Smessaert, Schehr and Artusio demonstrated a reduction in PONV after gastric decompression [55] whilst Burtles and Peckett showed a reduction in postoperative vomiting but no decrease in nausea when a nasogastric tube remained *in situ* in the postoperative period [8]. The persistence of nausea was presumably caused by continuous nasopharyngeal stimulation by the presence of the tube.

This early observation that gastric decompression reduced the incidence of postoperative vomiting was confirmed by a more recent study in patients undergoing cholecystectomy [32]. However, in a prospective study designed specifically to investigate this effect of gastric decompression and avoiding persistent nasopharyngeal stimulation by removal of an orogastric tube immediately at the end of surgery, Hovorka, Korttila and Erkola were unable to demonstrate any benefit in 201 women undergoing abdominal hysterectomy [30].

OTHER FACTORS DURING ANAESTHESIA

It has been suggested recently that patients exposed to positive intraoperative suggestions during general anaesthesia may have lower rates of vomiting and nausea after operation compared with those patients exposed to non-suggestive comments played via earphones during anaesthesia [63]. However, this suggestion awaits confirmation in larger studies.

Whilst it has been suggested that the duration of anaesthesia is associated with the incidence of postoperative emesis, this factor cannot be extricated from the duration of surgery and such suggestions can only be speculative [38].

Movement of the patient after operation may provoke nausea and vomiting in patients who have received opioids [13, 44]. Kamath and colleagues found that 66% of patients who identified a cause for postoperative nausea blamed movement [34], and that these patients had a particular susceptibility to motion sickness. They suggest limiting patient movement after operation.

POSTOPERATIVE PAIN

Pain *per se* is associated with nausea and vomiting and relief of pain by optimum administration of opioids results in a reduction in the incidence of nausea, although excessive doses of opioids may provoke opioid-induced emesis. In 1978, Anderson and Krohg [2] found that 90% of patients with nausea after abdominal surgery also had accompanying pain, and that in 80% of these patients, relief of pain by injection of opioid resulted also in abolition of nausea.

Administration of optimum doses of morphine, administered by patient-controlled analgesia, does not result in greater degrees of emesis than morphine given 4-hourly by i.m. injection [50].

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CURRENT MANAGEMENT OF POSTOPERATIVE NAUSEA AND VOMITING

D. J. ROWBOTHAM

Before specific antiemetic agents became available, various techniques, including olive oil [51] and insulin–glucose infusions [122], were reported to be effective in reducing the incidence of postoperative nausea and vomiting (PONV). Robert Ferguson [51] described the use of olive oil in 1912. The oil was administered "by mouth immediately after partial restoration of consciousness" and he postulated that oil in the stomach "absorbed any ether that might be there". However, the effect of atropine was appreciated by Brown-Sequard as early as 1883 when he wrote " in the very great majority of cases, the addition of a certain amount of atropine to the morphine prevents the vomiting and also the nausea occasioned by morphine alone" [48].

Antiemetic drugs are now the mainstay of therapy for PONV and this article reviews those in common use. Clearly, many factors affect the incidence of PONV and it is difficult to compare data from different studies. In this review, placebo-controlled studies of satisfactory design only are described. However, some important investigations into the efficacy of older antiemetics were not, by modern standards, well controlled. These studies are included in this review but any shortcomings in design are identified. To aid comparison, many studies are summarized in tables. For clarity, the nature of the anaesthetic agents used in each study is not listed in the tables. However, studies are arranged in chronological order which gives some indication of the type of anaesthetic technique used. In most tables, efficacy is presented as a comparison with placebo. This has been calculated as the percentage difference in the incidence of PONV between placebo and treatment or, if not available, the incidence of vomiting only. The majority of studies have been concerned with the prevention of PONV; only a few have investigated treatment.

There are several types of antiemetics used in the management of PONV. Gastrointestinal prokinetic drugs with antidopaminergic actions (e.g. metoclopramide, domperidone) are antiemetics. Phenothiazines (e.g. prochlorperazine, perphenazine) and butyrophenones (e.g. droperiodol) have antiemetic properties resulting also from antidopaminergic actions. Central anticholinergic action is associated with antiemetic activity and this is seen not only in classical anticholinergic drugs such as hyoscine and atropine, but also in some antihistamine receptor-type 1 antagonists (e.g. cyclizine). It may be that the anticholinergic effects of these drugs are responsible for their antiemetic activity [56].

The pharmacokinetics, efficacy compared with placebo, and side effects, with an emphasis on the postoperative period are reviewed for each antiemetic. Comparative studies are then considered. The effects of 5-HT_3 antagonists such as ondansetron [70] on PONV are not considered as this subject is reviewed in detail elsewhere [114].

GASTROINTESTINAL PROKINETIC DRUGS

Gastrointestinal prokinetic drugs enhance gastric and upper intestinal motility. Metoclopramide and domperidone act primarily as antidopaminergics [22, 62] and therefore have antiemetic activity, particularly at the chemoreceptor trigger zone. Direct action on the gastrointestinal tract is likely to have some antiemetic effect but the relative importance of this is not clear. Metoclopramide has some antagonistic effect at the 5-HT_3 receptor which may account for some of its antiemetic activity, particularly at high doses [53]. Cisapride is another effective gastrointestinal prokinetic drug but has no antidopaminergic effect and therefore little antiemetic activity [85].

Metoclopramide

Metoclopramide was developed in France in the early 1960s and is related structurally to procainamide (2-methoxy-5-chloroprocainamide). It has been used extensively in the treatment and prevention of PONV in the last 30 years and there is an extensive literature on its efficacy.

Pharmacokinetics. Metoclopramide was absorbed rapidly after oral administration to volunteers. The mean (range) time to peak concentration (*t*Cmax) was 0.9 (0.5–1.25) h [112]. However, there was substantial variation between individuals in first-

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KEY WORDS

Gastrointestinal tract. Pharmacology: phenothiazines, anticholinergics, butyrophenones, antihistamines. Vomiting: nausea.

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TABLE I. *Studies demonstrating efficacy of metoclopramide in the prevention of PONV (% reduction in incidence of PONV compared with placebo). Paed./eyes = Paediatric ophthalmic; Elect. CS = elective Caesarean section; Maj. gynae. = major gynaecological; Min. gynae. = minor gynaecological; Orthop. = orthopaedic; Upper abdo.+NGT = upper abdominal with postoperative nasogastric tube. Before = Given as premedication or at induction of anaesthesia; End = given at the end of anaesthesia. *At 1–3 h after anaesthesia only*

Reference	Year	Surgery	Dose (mg)	Route	Time	Reduction (%)
[59]	1967	Min. gynae.	10	I.m.	End	80
[41]	1968	Upper abdo.+NGT	20	I.v.	End	40
[128]	1969	"High risk"	Various	I.v.	End	50
[29]	1969	Min. gynae.	20	I.m.	End	75
[3]	1974	Min. gynae.	10–20	I.m.	Before	37–60
[33]	1979	Elect. CS	10	I.v.	Before	43
[39]	1980	Orthop.	20	Oral	Before	77*
[69]	1986	Orthop./female	20	I.v.	End	30
[27]	1987	Elect. CS	0.15 kg^{-1}	I.v.	Post-clamp	67
[92]	1988	Min. gynae.	10	Oral	Before	58
[21]	1990	Paed./eyes	0.15 kg^{-1}	I.v.	End	37
[17]	1990	Maj. gynae.	10	I.v.	Before	41

pass metabolism resulting in a wide range of peak plasma concentrations and oral bioavailability (32–97%) [62]. In a study comparing oral and i.m. absorption in volunteers, *t*Cmax values were similar (oral 97.5 min; i.m. 91.9 min) [28]. Elimination half-life is approximately 4 h and plasma clearance is similar to hepatic plasma flow [62]. Rapid redistribution of metoclopramide after i.v. administration has been reported ($T^{\alpha}_{\frac{1}{2}} = 4.9$ min) [8].

Clinical use. Many workers have investigated the efficacy of metoclopramide in the prevention of PONV and it is surprising that approximately 50% of studies have shown it to be no more effective than placebo. Table I summarizes those studies in which metoclopramide was effective and table II those in which it was not effective. Although it is difficult to compare studies directly, it may be possible to draw some conclusions from these data. I.v. administration at induction of anaesthesia appears to be associated with failure (two successes, five failures). Perhaps this is not surprising in view of the rapid redistribution of metoclopramide after i.v. administration [8] resulting in low plasma concentrations in the postoperative period. The recommended dose for metoclopramide in PONV is 10 mg [4] but these data show that 20 mg may be more effective. Oral administration has been shown to be effective [39, 92] but metoclopramide 5 and 10 mg orally was ineffective in patients after outpatient laparoscopy [101]. However, seven treatment groups were included in this study (including various doses of droperidol), and there was a trend for metoclopramide to be effective (65% nausea or vomiting with placebo; 45% with metoclopramide 10 mg). Only 20 patients were included in each group and it is likely that the power of this study was insufficient to be certain of these negative findings.

Side effects. The most important side effects associated with the use of metoclopramide are extrapyramidal reactions. The incidence of extrapyramidal reactions with metoclopramide reported to the Committee on Safety of Medicines (CSM) has been reviewed by Bateman, Rawlins and Simpson [9]. The reported rate for dystonia was 28.6 per million prescriptions; 94% of these occurred within the first 72 h and were more frequent in females and young patients. For example, the incidence in females aged 12–19 yr was 1 in 5000. The authors stress that this incidence is likely to be a gross underestimation as under-reporting of adverse drug reactions is known to be 90–99%. Dystonia has been reported [116] after anaesthesia but the incidence is not known. Parkinsonian reactions occur usually in the elderly and are associated with a more prolonged exposure to metoclopramide. The neuroleptic malignant syndrome, usually associated with drugs such as phenothiazines and butyrophenones, can develop in patients receiving metoclopramide [54].

Sedation occurs in approximately 10% of patients receiving long-term therapy [62] and delayed recovery from anaesthesia has been reported [82], but rarely occurs at normal doses when used for PONV.

Dundee and Clarke [44] reported a significant incidence of restlessness after metoclopramide 10 and 20 mg i.m. administered as premedication. Extreme agitation in this context is rare but Caldwell, Rains and McKiterick [24] reported severe dysphoria, agitation and akathisia in a 21-yr-old female who

TABLE II. *Studies failing to demonstrate significant efficacy of metoclopramide compared with placebo in the prevention of PONV. OP laps. = Outpatient laparoscopy; Maj. gynae. = major gynaecological; Min. gynae. = Minor gynaecological; Orthop. = Orthopaedic; Upper abdo. = upper abdominal; Orthop./spinal = orthopaedic under spinal anaesthesia; NGT = nasogastric tube. Before = Given as premedication or at induction of anaesthesia; End = given at the end of anaesthesia*

Reference	Year	Surgery	Dose (mg)	Route	Time
[41]	1968	Upper abdo., no NGT	20	I.v.	End
[50]	1970	Min. gynae.	10–20	I.v.	Before
[119]	1972	Min. gynae.	10	I.m.	End
[44]	1973	Min. gynae.	10–20	I.m.	Before
[73]	1979	Orthop./ female	10	I.v.	End
[33]	1979	Min. gynae.	10	I.v.	Before
[124]	1984	Orthop./ spinal	10	I.v.	Before
[32]	1984	Min. gynae.	10	I.v.	Before
[133]	1985	Min. gynae.	10	I.v.	Before
[89]	1986	Maj. gynae.	10	I.v.	End
[131]	1987	Ophthalmic	0.15 kg^{-1}	I.v.	End
[101]	1989	OP laps.	5–10	Oral	Before

had received metoclopramide 10 mg and glycopyrronium 0.2 mg as premedication. Her symptoms were reversed by benztropine. Similar symptoms were reported in three patients who had received both metoclopramide and droperidol as preoperative medication for eye surgery [7].

I.v. administration of metoclopramide may be associated with significant cardiovascular side effects. Four patients suffered significant episodes of hypotension when metoclopramide 10 mg was given i.v. during dural closure after the use of hypotensive agents had ceased [102]. This was confirmed in 16 patients undergoing similar surgery when metoclopramide 10 mg, given 20 min before the end of surgery, resulted in a mean decrease of 20 % in both systolic and diastolic pressures [104]. Mean time of maximal decrease was 44 s after administration. Ellis and Spence reported a significant increase in heart rate in patients given metoclopramide i.v. before induction of anaesthesia [50]. Supraventricular tachycardia after i.v. administration occurred also in a patient scheduled for laparoscopic tubal ligation [15]. Paradoxically, severe bradycardia has occurred also after i.v. metoclopramide [137]. It is therefore recommended that i.v. administration of metoclopramide should be over 1–2 min [4]. In view of the efficacy data presented in tables I and II, and these potential side effects, perhaps the indications for i.v. administration of metoclopramide are few, particularly at induction of anaesthesia. However, significant supraventricular ectopics have been reported after i.m. administration also [120].

Domperidone

Domperidone is less likely to cross the blood–brain barrier than metoclopramide and therefore extrapyramidal reactions should not occur [22]. This was the logic responsible for the development and introduction into clinical practice of this drug. Unfortunately, extrapyramidal reactions with domperidone have been reported [88] although less frequently than with metoclopramide. Only a few studies have compared domperidone with placebo in the prevention of PONV and most of these showed no significant effect [73, 89, 124, 133]. However, efficacy was demonstrated in patients undergoing Caesarean section [33].

Further work on domperidone was prevented by the withdrawal of the parenteral preparation. This was the result of several reports of serious cardiac arrhythmias after i.v. administration of large doses, usually for chemotherapy-induced emesis [25, 58, 67, 100, 113]. Domperidone in now available only as an oral and rectal preparation and interest in its use for PONV has waned.

PHENOTHIAZINES

Phenothiazines were synthesized originally in the late 19th century by chemists working in the dye industry [6]. In the late 1930s promethazine, a phenothiazine derivative, was found to have profound hypnotic properties and was introduced into anaesthetic practice. Promethazine is still administered as premedication and significant effects on PONV have been demonstrated [16, 23, 65]. However, its sedative action limits its use considerably.

Charpentier synthesized chlorpromazine in 1949 [6] and it was introduced into clinical practice shortly afterwards. Its many side effects, particularly sedation and hypotension, limit its use as an antiemetic also, but efficacy in the prevention of PONV has been demonstrated [2, 19, 26, 42, 65, 72, 77].

Prochlorperazine and perphenazine are phenothiazine derivatives which have been used extensively in the management of PONV.

Prochlorperazine

Pharmacokinetics. The pharmacokinetics of prochlorperazine were first described in detail in 1987, over 30 years after its introduction into anaesthetic practice. After i.v. administration to volunteers of prochlorperazine 12.5 mg, mean (SEM) elimination half-life was 6.8 (0.7) h, volume of distribution 1548 (155) litre and plasma clearance 2.7 (0.3) litre min^{-1} [125]. Surprisingly, oral bioavailabilty was poor; after 25 mg orally, plasma prochlorperazine was detectable in only 50 % of subjects (lower limit of detection of assay 1 ng ml^{-1}) and $tC\text{max}$ was 1.5–5 h.

Clinical use. Prochlorperazine was introduced for the prevention of PONV in the 1950s [23], but there are only limited data on its efficacy. Studies comparing prochlorperazine with placebo are summarized in table III. In 1959, Robbie was able to demonstrate only a trend towards efficacy [111]. However, vomiting, and not nausea, was investigated and the incidence of vomiting was surprisingly low for such an early study (control 19 %, prochlorperazine 11 %). Other investigations, some more recent, have shown prochlorperazine to be effective in the prevention of PONV [64, 65, 128]. However,

TABLE III. *Studies investigating the effect of prochlorperazine on PONV (% reduction in incidence of PONV compared with placebo). Gen. surg. = General surgery; Gynae. lap. = gynaecological laparoscopies. Before = Given as premedication or at induction of anaesthesia; End = given at the end of anaesthesia. *No statistics available; ns = no significant effect*

Reference	Year	Surgery	Dose (mg)	Route	Time	Reduction (%)
[111]	1959	Various	12.5	I.m.	End	Trend only
[65]	1960	Gen. surg.	12.5	I.v.	Before, end	43* 41*
[128]	1969	Various	12.5	I.m.	End	50
[34]	1989	Gen. surg.	10	I.v.	Before	ns
[64]	1989	Gynae. lap.	5	I.v.	End	73

TABLE IV. *Studies investigating the effect of perphenazine on PONV (% reduction in incidence of PONV compared with placebo). Min. gynae. = Minor gynaecological. Before = Given as premedication or at induction of anaesthesia; End = given at the end of anaesthesia. *No statistics available*

Reference	Year	Surgery	Dose (mg)	Route	Time	Reduction (%)
[95]	1958	Various	5	I.m.	Before and 6-hourly	65
[117]	1958	Various	5	I.m.	End	67
[111]	1959	Various	5	I.m.	End	63
[109]	1960	Min. gynae.	5	I.m.	Before	73*
[59]	1967	Min. gynae.	5	I.m.	End	90

Cramb, Fargas-Babjak and Hirano [34], showed no significant effect when prochlorperazine 10 mg i.v. was given 10 min after induction of anaesthesia in patients undergoing major general surgery. The duration of anaesthesia was not reported in this study but it is likely that patients were emerging from anaesthesia some time after prochlorperazine administration.

Prochlorperazine 10 mg has been shown to be effective in the treatment of established vomiting after anaesthesia [83]. The incidence of continued vomiting 0.5–1 h after prochlorperazine was only 7% compared with 70% after saline. Antiemetic effects continued for at least 4 h (13% vomiting compared with 50%).

Side effects. Side effects of any phenothiazine include, cholestatic jaundice, haematological abnormalities, skin sensitization, hyperprolactinaemia and neuroleptic malignant syndrome. However, these are rare, but sedation, extrapyramidal reactions and cardiovascular effects are important side effects in anaesthesia.

Acute dystonias have been reported after prochlorperazine; children, young adults and females are most frequently affected [10, 14, 106]. During the period 1967–1982, 104 extrapyramidal reactions were reported to the CSM, during which time there were an estimated 37 million prescriptions (2.8 per million) [10]. Most of these were acute dystonia–dyskinesia reactions and developed within 3 days of treatment. Approximately 25% of reactions occurred after a single parenteral dose. Porter and Jick investigated adverse drug reactions in 32812 patients admitted consecutively to hospitals in Boston, U.S.A. [106]. The incidence of extrapyramidal side effects associated with prochlorperazine was 0.3%. The relative proportions of patients receiving prochlorperazine in large (psychiatric indications) or smaller doses (PONV) are not clear, but no reactions were reported in patients receiving less than 10 mg. Akathisia was reported by five of eight volunteers who were given prochlorperazine 12.5 mg i.v. during a pharmacokinetic study [125].

The effect of prochlorperazine on recovery from anaesthesia has not been investigated extensively but early reports give some indication of its effects. Recovery was "prolonged" in two of 56 patients [65] receiving prochlorperazine compared with none of 53 receiving saline, and excess postoperative sedation in a small number of patients was reported by Tornetta [128]. However, Robbie reported a mean recovery time of 17.1 min in patients receiving prochlorperazine compared with a control value of 18.5 min [111].

Perphenazine

Pharmacokinetics. The pharmacokinetics of perphenazine have been investigated in 18 patients and five volunteers [60]. After i.v. administration of 5 or 6 mg, mean (range) elimination half-life was 9.4 (8.4–12.3) h, plasma clearance 107 (49–183) litre h^{-1} and volume of distribution 20.2 (9.8–34.6) litre kg^{-1}. Oral bioavailability was poor. After a single oral dose of 6 mg, no perphenazine was detectable in plasma (lower limit of assay detection 0.2 $\mu g\ ml^{-1}$). However, perphenazine was absorbed well after i.m. administration.

Clinical use. Only a small number of studies investigating the efficacy of perphenazine in PONV is available in the literature [20, 40, 59, 95, 109, 111, 117]. Those which were placebo-controlled are summarized in table IV. Most of these studies were performed 30 years ago but the results are impressive. Perphenazine was effective in all these studies and the percentage change in the incidence of PONV compared with placebo was large. The design of some of these studies would be considered poor by modern standards but large numbers of patients were investigated.

Side effects. There can be no doubt that perphenazine is an effective antiemetic but there is a general impression that it is more likely to cause extrapyramidal side effects than other antiemetics [66]. Is there any evidence for this? Braly and Moore [20] gave perphenazine to 2794 patients undergoing general and local anaesthesia for a wide variety of surgical procedures. Four cases (0.14%) of acute dystonia were reported. Robbie [111] gave perphenazine to 166 patients and prochlorperazine to 105 patients. Acute dystonias did not occur after prochlorperazine but two cases were described after perphenazine (1.2%). No cases of dystonias were reported in the studies summarized in table III describing the effects of prochlorperazine. Furthermore, many cases of extrapyramidal reactions, especially in young patients, were reported in the literature when perphenazine was first used extensively as an antiemetic for PONV [37, 71, 93, 108, 123]. It is likely therefore that the incidence of extrapyramidal reactions is relatively greater with

TABLE V. *Studies demonstrating efficacy of droperidol in the prevention of PONV (% reduction in incidence of PONV compared with placebo). Paed./eyes = Paediatric ophthalmic; Paed./ortho. = paediatric orthopaedic; Elect. CS = elective Caesarean section; Maj. gynae. = major gynaecological; Min. gynae. = minor gynaecological; Orthop. = orthopaedic. Before = Given as premedication or at induction of anaesthesia; End = given at the end of anaesthesia. *Dose (mg) per 70 kg*

Reference	Year	Surgery	Dose (mg)	Route	Time	Reduction (%)
[103]	1973	Maj. gynae.	5.0	I.v./i.m.	Before	46
[136]	1977	Min. gynae./urological	5.0	I.m.	Before	55
[73]	1979	Female orthop.	1.25	I.v.	End	55
[110]	1981	Paed./orthop. (11–15 yr)	0.35*	I.v.	End	51
[97]	1982	Min. gynae.	2.5	I.v.	Before	56
			5.0	I.v.	Before	60
[1]	1983	Paed./eyes	5.25*	I.v.	End	50
[99]	1984	Min. dental	0.25	I.v.	Before	72
[115]	1984	Elect. CS/spinal	2.5	I.v.	After delivery	70
[74]	1985	Female orthop.	2.5	I.m.	Before	41
			1.25	I.v.	End	37
[130]	1985	Dental	1.0*	I.v.	Before	33
[69]	1986	Female orthop.	1.25	I.v.	End	58
[89]	1986	Maj. gynae.	2.5	I.v.	End	35
[101]	1989	Min. gynae.	0.7*	I.v.	Before	66
			1.4*	I.v.	Before	75
[78]	1990	Paed./eyes	5.25*	I.v.	End	27

perphenazine, particularly compared with prochlorperazine.

Whether or not this effect is more frequent when compared with metoclopramide is open to question. Metoclopramide or perphenazine was given to approximately 200 patients undergoing gynaecological laparotomies [82] and to 584 women in labour [87], and no extrapyramidal side effects were reported with either agent.

Perphenazine has been shown to delay recovery from anaesthesia. Mean recovery time after various surgical procedures was 17 min in a placebo group compared with 27 min in the group receiving perphenazine [117]. In a comparative study by Robbie [111], mean recovery times were 18.5 min (control group), 22.3 min (perphenazine) and 17.1 min (prochlorperazine). Unfortunately, no statistical analysis is available for these data but it would tend to support the view that more sedation occurs with perphenazine compared with prochlorperazine when used in doses appropriate for PONV.

BUTYROPHENONES

Many butyrophenones are potent neuroleptics but droperidol is the only drug of this class used extensively in anaesthesia.

TABLE VI. *Studies demonstrating no effect of droperidol compared with placebo in the prevention of PONV. Paed./eyes = Paediatric ophthalmic; Min. gynae. = minor gynaecological. Before = Given as premedication or at induction of anaesthesia. *Dose (mg) per 70 kg*

Reference	Year	Surgery	Dose (mg)	Route	Time
[96]	1970	Min. gynae.	5, 10	I.m.	Before
[99]	1984	Min. dental	1.25	I.v.	Before
[32]	1984	Min. gynae.	1.25	I.v.	Before
[61]	1986	Paed./eyes	3.5*	I.v.	Before
[131]	1987	Adult eyes	2.45	I.v.	Before
[101]	1989	Min. gynae.	0.35*	I.v.	Before
[90]	1989	Min. gynae.	1.25	I.v.	Before

Droperidol

Pharmacokinetics. After i.v. administration of droperidol, the redistribution half-life is approximately 10 min [35], elimination half-life approximately 2 h and plasma clearance approximately 15 ml min^{-1} kg^{-1} [35, 52]. A study investigating the pharmacokinetics of droperidol 10 mg in patients undergoing anaesthesia suggested that elimination half-life, plasma clearance and volume of distribution were not influenced significantly by volatile anaesthetic agents (halothane, enflurane), body weight (48–90 kg) or age (14–65 yr) [80]. Droperidol is well absorbed after oral administration [Janssen Pharmaceuticals, personal communication] and i.m. absorption is rapid (*t*Cmax approximately 30 min [35]). Droperidol is metabolized extensively (1% unchanged in urine) and significant biliary excretion has been described (approximately 10% appearing in faeces) [35].

Clinical use. The majority of studies have found that droperidol is more effective than placebo in the prevention of PONV (table V). Efficacy has been demonstrated after administration of droperidol both before and at the end of surgery. I.m. administration has been shown to be effective [74, 136], and also combined i.v. and i.m. administration at induction of anaesthesia [103].

Studies failing to show efficacy of droperidol are summarized in table VI. Droperidol was administered at induction of anaesthesia in every study suggesting that, despite the evidence in table V, efficacy will be improved if droperidol is administered towards the end of surgery. Van den Berg and colleagues [131] failed to show an effect not only of droperidol but also of metoclopramide and prochlorperazine after ophthalmic surgery. The study design was complicated by the inclusion of groups who were denied fluids after operation. Data reported by Hardy and coworkers [61] indicated a trend towards reduction of vomiting in the recovery room

TABLE VII. *Comparison of recovery times (min) after i.v. droperidol and placebo. *Dose (mg) per 70 kg*

Reference	Year	Dose (mg)	Mean recovery time		P
			Placebo	Droperidol	
[32]	1984	1.25	3	6	< 0.01
[99]	1984	1.25	8	10	< 0.05
[61]	1986	3.5*	27	34	0.036

(placebo 23% ($n = 7$), droperidol 6% ($n = 2$)) but statistical significance was not achieved. A similar trend was reported by Melnick and colleagues [90] (placebo, seven patients nauseated; droperidol 1.25 mg, four patients). It is likely that insufficient patients were investigated in these studies to be confident of a negative result. Therefore, many of the studies which failed to show efficacy of droperidol can be criticized. However, the failure of droperidol in preventing nausea after minor gynaecological surgery was shown convincingly by Cohen, Woods and Wyner [32] (placebo 70%; droperidol 1.25 mg 72%).

Because of the side effects of droperidol, there has been some interest in discovering the most effective dose. The summaries of both successful and unsuccessful studies shown in table V and VI show that both relatively large doses have been associated with failure and relatively small doses with success. Many factors affect PONV including age, sex, procedure and anaesthetic technique and clearly it is difficult to draw conclusions based on comparisons between these studies. However, comparisons have been made within single studies [97, 99, 101]. Two groups have investigated patients undergoing minor gynaecological surgery. Mortensen [97] gave droperidol 2.5 and 5 mg i.v. at induction of anaesthesia and reduced the incidence of nausea by 56 and 60%, respectively. After outpatient laparoscopies, Pandit and colleagues [101] gave 5, 10 and 20 μg kg^{-1} (0.35, 0.7 and 1.4 per 70 kg). The 10- and 20-μg kg^{-1} doses were very effective (66 and 75% reduction in nausea, respectively). In this study of relatively few patients, droperidol 5 μg kg^{-1} reduced nausea by 33%, but this was not statistically significant.

O'Donovan and Shaw [99] reported curious data after day-case dental surgery. Patients were given droperidol 1.25 mg, droperidol 0.25 mg or placebo, at induction of anaesthesia in a double-blind, placebo-controlled study. Surprisingly, it was concluded that droperidol 0.25 mg reduced nausea whilst droperidol 1.25 mg had no significant effect. The incidence of PONV was measured by staff observations and a patient questionnaire. There was a low incidence of vomiting (five patients (11%) after placebo) but the incidence of nausea reported by patients was greater (16 patients (35%) after placebo). Both doses of droperidol tended to reduce the incidence of both nausea and vomiting but the only significant difference found by the authors was the effect of droperidol 0.25 mg on the incidence of nausea reported by the patients during their hospital stay. It cannot be concluded reliably from this study of relatively low power that droperidol 1.25 mg was less effective than droperidol 0.25 mg.

The literature does not enable us to make firm conclusions as to the most appropriate dose of droperidol for prevention of PONV but it is likely that droperidol is an effective antiemetic, even at relatively small doses.

Loeser and colleagues [83] investigated the efficacy of droperidol 5 mg i.m. in the treatment of vomiting in the recovery room after standardized anaesthesia. Compared with placebo, emesis scores were significantly improved after 0.5–1 h. Peak effectiveness was at 4 h and a significant difference from placebo could be demonstrated even after 24 h.

Side effects. The side effects of butyrophenones are very similar to those associated with phenothiazines. Several workers have reported a statistically significant delay in recovery from anaesthesia after droperidol [32, 61, 97, 99]. Time to recovery was not defined in precisely the same manner in these studies but it is informative to compare these data (table VII). In addition, Mortensen [97] found that, after minor gynaecological surgery and droperidol 2.5 or 5.0 mg i.v., significantly more patients were rated as excessively drowsy in recovery but there was no difference between placebo and droperidol in duration of stay in the recovery ward. It may be argued, therefore, that although recovery may be significantly delayed, the differences may not be important clinically. However, the effect of droperidol has been demonstrated later in the postoperative period. In the same study, Mortensen found an increase in excessive drowsiness reported by patients after discharge to the ward of approximately 50% ($P < 0.001$). Valanne and Korttila [130] investigated recovery of young healthy patients after anaesthesia for minor dental surgery who were given droperidol 0.014 mg kg^{-1} (1 mg/70 kg) i.v. or placebo. Although recovery times were similar (approximately 14 min), ability to perform psychomotor speed tests was impaired significantly in patients who received droperidol.

The addition of droperidol 0.2 mg kg^{-1} to trimeprazine given as oral premedication to children was associated with a significant increase in preoperative sedation [71] and recovery time after anaesthesia [132].

Extrapyramidal reactions are recognized side effects of droperidol. The true incidence when used to prevent PONV is not known, but it is relatively rare. For example, none of the studies discussed above reported such effects. Dupre and Stieglitz [49] described extrapyramidal reactions in four children after relatively large doses (0.1–0.17 mg kg^{-1} (7–11.9 mg/70 kg) as premedication). However, extrapyramidal effects have been reported also after small doses (e.g. 0.65 mg) [91]. It is important to realize that these reactions can occur some time after the administration of droperidol. For example, a 10-yr-old boy, premedicated with droperidol 0.16 mg kg^{-1} before halothane anaesthesia for removal of dental cyst, developed opisthotonos and oculogyric spasms 14 h after anaesthesia [49]. Melnick [91] described a 24-yr-old lady who underwent outpatient laparoscopy and was given droperidol 0.65 mg i.v. for prevention of PONV. She was discharged home only to be readmitted later that day with acute dystonia (spasm of neck and tongue muscles) which responded to diphenhydramine. Acute akathisia occurring with droperidol taken with metoclopramide has been described also [7].

Morrison, Clarke and Dundee assessed apprehension, excitement and restlessness immediately before induction of anaesthesia in patients undergoing minor gynaecological surgery after droperidol premedication [96]. After droperidol 5 mg i.m., 19 % complained of marked apprehension (placebo 8 %) and 30 % of excitement or restlessness (placebo 2 %). The incidence of the latter was increased with droperidol 10 mg (45 %).

Melnick and colleagues [90] followed-up their case report with a fascinating study. Patients received either droperidol 1.25 mg or saline at induction of standardized anaesthesia for minor gynaecological surgery. No extrapyramidal side effects occurred on recovery and all were discharged home. A nurse, blinded to the treatment groups, telephoned the patients at home 24–36 h after surgery. Twenty-three percent of patients complained of unpleasant sensations of anxiety during the day and night after discharge. All these patients had received droperidol; no patient who received placebo experienced such symptoms. These data, particularly if confirmed by others, must raise doubts as to the suitability of droperidol as an antiemetic in day-case surgery.

Droperidol has alpha-adrenergic blocking properties and may cause hypotension when administered during anaesthesia. Surprisingly, little attention has been paid to this and its incidence and severity is not known. It is not likely to be a significant problem when given in relatively low doses to fit patients.

ANTICHOLINERGICS

Hyoscine or scopolamine (tropic acid ester of scopine) and hyoscyamine or atropine (tropic acid ester of tropine) are centrally and peripherally acting anticholinergics used extensively in anaesthetic practice. They are derived from solanaceous plants and have antiemetic activity.

Hyoscine

Racemic mixtures of hyoscine occur naturally but only the laevoisomer is active pharmacologically.

Pharmacokinetics. Pharmacokinetic data on hyoscine are limited, despite its widespread use in medicine. Plasma hyoscine concentrations are difficult to measure but using an enzyme immunoassay technique, pharmacokinetic values after i.v. administration (5 $\mu g\ kg^{-1}$) in patients undergoing Caesarean section have been reported [105]. Mean (SD) distribution and elimination half-life were 5.0 (3.2) min and 1.9 (2.2) h, respectively, plasma clearance 14.4 (17.4) ml kg^{-1} min^{-1} and volume of distribution 1.1 (0.6) litre kg^{-1}. Mean (SEM) elimination half-life, plasma clearance and volume of distribution in six male volunteers were 4.5 (1.7) h, 65.3 (5.2) litre h^{-1} and 1.4 (0.3) litre kg^{-1}, respectively [107]. After i.m administration in four of these volunteers, absorption was rapid and reliable (*t*Cmax 10 min in each volunteer). Oral bioavailability of hyoscine 0.4 mg in six volunteers was 10.7–48.2 % and mean (range) *t*Cmax was 0.78 (0.33–2.0) h [108]. A similar range of *t*Cmax values was reported by Muir and Metcalfe [98].

I.m. administration. Hyoscine has been used for many years as premedication, often administered with morphine or pethidine. The efficacy of hyoscine in this situation as an antiemetic has not been investigated extensively under controlled conditions, but two studies from Belfast demonstrated clear efficacy [30, 47]. When administered with pethidine 100 mg, hyoscine 0.4 mg reduced the incidence of vomiting and retching in the 6 h after anaesthesia from 34 % to 20 %. It was even more effective in the first hour after anaesthesia (23 % *vs* 5 %). Similar data were obtained when hyoscine was given with morphine 10 mg. Hyoscine was more effective than atropine but there was a tendency for patients to be more drowsy on induction of anaesthesia and for delay in recovery from anaesthesia. Tachycardia was not reported.

Transdermal administration. The development of a transdermal preparation of hyoscine is an attempt to alleviate the problems of short plasma half-life and dose-dependent side effects. Plasma concentrations of hyoscine during transdermal administration are small. Using a radioreceptor assay, plasma hyoscine was detected in only four of 12 subjects (mean concentration 0.42 nmol $litre^{-1}$ after 8 h) [98]. These data reflect not only the small plasma concentrations of hyoscine achieved during transdermal administration, but also the need for a more sensitive assay. However, only relatively small concentrations are required as it has been shown that the antiemetic effect occurs at a urinary excretion rate of hyoscine $< 1\ \mu g\ h^{-1}$ compared with dry mouth ($> 1\ \mu g\ h^{-1}$), drowsiness ($3\ \mu g\ h^{-1}$) and tachycardia ($> 5\ \mu g\ h^{-1}$) [121].

Transdermal hyoscine has been used effectively in the prevention of motion sickness but dry mouth (about 67 %) and drowsiness (16 %) have been reported [31, 36]. Its use in the prevention of PONV has been reported by several authors. Most double-blind, placebo-controlled studies have found transdermal hyoscine to be more effective than placebo after surgery. An impressive reduction in the incidence of severe nausea and vomiting was reported after day-case laparoscopy [5]; the incidence of PONV in the placebo group was high (62 %, placebo; 37 %, transdermal hyoscine). Efficacy after major gynaecological surgery and papaveretum analgesia was demonstrated also; the incidence of vomiting and severe nausea in the placebo group was 100 % (transdermal hyoscine 68 %) [129]. After Caesarean section under extradural analgesia followed by morphine 4 mg extradurally, transdermal hyoscine reduced the incidence of nausea and vomiting by approximately 50 %, 2–10 h after surgery [76]. No effect was demonstrable at 10–24 h. However, transdermal hyoscine was very effective for 24 h in patients receiving morphine extradurally after major gynaecological surgery [84]. Efficacy has been claimed in patients after major gynaecological surgery receiving morphine by patient-controlled analgesia [63]. Although there was a significant decline in severity of nausea compared with placebo and fewer patients demanded escape antiemetic therapy at 6 and 24 h after surgery, there was no significant difference in the incidence of nausea or vomiting. It may be that the power of this study was insufficient to detect a difference reliably. Steady-state concentrations are not achieved for at least 5 h after application of the patch [31] and this may have been an important factor in the equivocal findings, as patches were applied at induction of anaesthesia. Similar results were reported by Semple and colleagues who applied the patch 2 h before anaesthesia [118].

Two double-blind, placebo-controlled studies have failed to show any significant effect of transdermal hyoscine compared with placebo. Tigerstedt, Salmela and Aromaa applied the patch only 50 min before anaesthesia in patients undergoing a wide range of surgical procedures [126]. (Patches were applied several hours before anaesthesia in several of the studies demonstrating efficacy [5, 129, 135].) However, Koski and colleagues failed to show efficacy of transdermal hyoscine applied on the evening before surgery compared with placebo [75]. Unfortunately, premedication (promethazine or flunitrazepam), postoperative analgesia (buprenorphine i.m. or sublingually, or oxycodone) and type of surgery (gynaecological, upper abdominal, thyroid, breast and others) and dose of intraoperative fentanyl were not controlled. Duration of anaesthesia varied widely also (20–337 min).

A significant incidence of dry mouth was reported by some authors [5, 63, 75, 76, 135] but not by others [126, 129]. Visual disturbances were relatively common also [5, 75, 126, 129]. Drowsiness was reported only by Bailey and colleagues in patients undergoing day-case laparoscopies [5]. In fact, the incidences of dry mouth, somnolence, amblyopia, mydriasis and dizziness were all increased significantly in this study. However, these effects, although significant statistically, were not significant clinically as the patients receiving transdermal hyoscine were discharged significantly earlier compared with the placebo group (mean (SD) 4.0 (1.3) h *vs* 4.5 (1.5) h, respectively; $P < 0.05$). This may have resulted from the significant improvement in the incidence of PONV in the transdermal hyoscine group.

Hyoscine-induced psychosis has been reported during administration of transdermal hyoscine, particularly in elderly patients [86]. However, it has occurred in a 10-yr-old child [31].

These data suggest that transdermal hyoscine has at least some efficacy in the prevention of PONV, particularly if applied several hours before surgery. Although relatively frequent, side effects are likely to be minimal and insignificant compared with other antiemetics.

Atropine

The pharmacokinetics of atropine have been investigated extensively and reviewed in great detail by Kanto and Klotz [68]. After i.v. administration, mean elimination half-life of 2.2–4.3 h, volume of distribution of 1.0–1.6 litre kg^{-1} and plasma clearance of 5.9–6.4 ml min^{-1} kg^{-1} have been reported. Distribution half-life after i.v. administration is small (mean 1.0–1.7 min) and Berghem and colleagues [13] calculated that only 5 % of the administrated i.v. dose remains in the circulation. There is considerable variability in absorption after i.m. administration in both *C*max and *tC*max. Mean *tC*max values of 0.33–1.59 h have been reported [68]. Atropine is well absorbed after oral administration.

Only a small number of studies have compared the effectiveness of atropine with placebo in the prevention of PONV and in most of these atropine was administered as a premedication. Riding [109] investigated the effect of atropine 0.3–1.2 mg given in combination with morphine 5–10 mg in patients undergoing minor gynaecological surgery. Compared with placebo, atropine had a significant effect on the incidence of nausea and retching when given alone in all doses (0.3, 0.6 and 1.2 mg). However, atropine 1.2 mg only reduced the incidence significantly when morphine 5 mg was administered. There was no significant effect in patients given morphine 10 mg. Investigators in Belfast compared the effect of atropine given with morphine 10 mg [30] and pethidine 100 mg [47]. After morphine premedication and methohexitone anaesthesia for short procedures, there was a trend, but not a statistically significant decrease, in the incidence of vomiting and retching during the first 6 h after operation in patients receiving atropine 0.6 mg. However, there was a significant decrease in the first hour (morphine only 28 %, morphine with atropine 12 %). After similar anaesthesia and surgery but with premedication with pethidine 100 mg, the incidence of vomiting and retching in the 6 h after surgery was 34 %. Atropine 0.6 mg had no effect on this incidence (30 %). Tachycardia was associated with the use of atropine in these studies but delayed recovery from anaesthesia was not reported.

Atropine is not used after anaesthesia in the management of PONV because of its cardiovascular effects. However, many workers investigating the efficacy of antiemetics have used atropine during and before anaesthesia and its likely effect on the incidence of PONV should be considered when assessing their data. However, the effect of atropine may not be great after i.v. administration because of its rapid redistribution half-life.

ANTIHISTAMINES

Drugs of several types (e.g. ethanolamines, piperazines, phenothiazines) exhibit histamine type-1 receptor antagonist activity and many are antiemetics. The use of promethazine (a phenothiazine) has been described above. Many antihistamines have been used for the prevention of motion sickness but only cyclizine has been used extensively for PONV.

Cyclizine

Cyclizine is a piperazine derivative. It has antimuscarinic actions also, and it is possible that the antiemetic activity of this and other antihistamines

TABLE VIII. *Studies investigating the effect of cyclizine on PONV (% reduction in incidence of PONV compared with placebo). Min. gynae = Minor gynaecological. Before = Given as premedication or at induction of anaesthesia; ? = not stated. *No statistics available; ns = no significant effect*

Reference	Year	Surgery	Dose (mg)	Route	Time	Reduction (%)
[38]	1955	Various	50	S.c.	End	24
[94]	1956	Various	50	I.m.	Before and 4-hourly	44
[127]	1956	Various	?	"Parenteral"	End	ns
[11]	1959	Various	50	?	?	39*
			100	?	?	39*
[111]	1959	Various	50	I.m.	End	ns
[109]	1960	Min. gynae.	50	I.m.	Before	77*

are largely the result of this antimuscarinic activity [56]. Surprisingly, little is known of the pharmacokinetics of cyclizine.

The efficacy of cyclizine in the prevention of PONV was investigated 30 years ago (table VIII). Most of these studies were poorly controlled, involved a variety of anaesthetic techniques and operations, and statistical analysis was sometimes lacking. However, patient numbers were large and some useful information can be extracted from them. Most workers demonstrated efficacy [11, 38, 94, 109].

Cyclizine has been shown to be effective in the treatment of established PONV. In a placebo-controlled, double-blind study, Bonica and colleagues [18] relieved PONV completely after rectal administration of cyclizine in 50.8 % of patients with severe symptoms (placebo 7.6 %). Efficacy was demonstrated also in patients with moderate or mild symptoms. In fact, cyclizine was associated with complete or partial relief in 93 % of all patients (placebo 60 %).

Extrapyramidal side effects are not associated with cyclizine. Sedation and dry mouth are a consequence of its antimuscarinic action but the importance of these side effects in the perioperative period is not know with any certainty. Moore and colleagues [94] described "occasional drowsiness" and Bellville, Bross and Howland [11] showed a slight tendency to delayed recovery from anaesthesia.

In light of these early studies and relative lack of side effects, perhaps the place of cyclizine in modern anaesthetic practice should be re-appraised.

ACUPUNCTURE

After a visit to mainland China, Dundee observed a woman in an antenatal clinic being treated for morning sickness by acupuncture [45]. This experience inspired several studies investigating its effect on PONV in Belfast, although attention was drawn to the efficacy of acupuncture at the same time by Fry [55]. Acupuncture for nausea is performed on the P6 or Neiguan point. This is situated between the tendons of the flexor carpi radialis and palmaris longus, 2 Chinese inches from the distal wrist skin crease. A Chinese inch is the width of the interphalangeal joint of the thumb [45].

Several studies have demonstrated efficacy of acupuncture in the prevention of PONV [43, 45, 57, 64]. After nalbuphine premedication and i.v. methohexitone anaesthesia for minor gynaecological surgery, preoperative acupuncture reduced PONV significantly in the first 6 h after surgery compared with controls (32 % *vs* 82 %) [45]. The incidence of PONV after acupuncture applied away from the P6 point was 90 %. The extraordinary high incidence of PONV by modern standards can presumably be explained by the use of agents such as nalbuphine and methohexitone, but the effect of acupuncture in these circumstances is clear. These data originate from 317 patients; the result of pooling data from previous studies. Such a study compared the effect of acupuncture with cyclizine 50 mg on PONV in patients undergoing identical anaesthesia and surgery [57]. Both manual and electrical acupuncture at the P6 point reduced the incidence of PONV significantly and had similar efficacy to cyclizine.

Using a more conventional anaesthetic technique, Ho and colleagues [64] demonstrated a beneficial effect of acupuncture in patients undergoing gynaecological laparoscopies. The incidence of PONV during the first 3 h after surgery was 44 % in the control group, 12 % after electroacupuncture and 12 % after prochlorperazine premedication. Stimulation of the P6 point by transcutaneous electrical stimulation was less effective (36 %).

However, other workers have failed to demonstrate efficacy [81, 134, 138]. In a well designed study, Lewis and colleagues [81] showed no effect in children undergoing strabismus surgery. However, acupuncture was administered by elasticated wrist bands ("Sea Bands") and not by conventional acupuncture techniques. Failure was reported also in children after tonsillectomy [138] but in this study acupuncture was administered during anaesthesia. Acupuncture may not be effective under these circumstances.

The use of acupuncture in the prevention of PONV has stimulated considerable debate but it seems clear that it is effective in some circumstances and, compared with conventional pharmacological therapies, is free from side effects. Further evaluation is beyond the scope of this article and the reader is referred to the review by Dundee and McMillan [46].

COMPARATIVE STUDIES

An appreciation of the relative efficacies of antiemetic drugs used in the management of PONV is important, particularly when side effects can be significant. The literature is not of great help in this regard but it is possible to draw some conclusions.

TABLE IX. *Comparisons of metoclopramide (M) and droperidol (D). Orthop. = Orthopaedic; Min. gynae. = minor gynaecological; Maj. gynae. = major gynaecological. *Not statistically significant (but see text); ns = no significant difference. NR = Not recorded*

Reference	Year	Surgery	Dose (mg)		Result	Recovery from anaesthesia
			M	D		
[73]	1979	Female orthop.	10	1.25	D > M	D > M
[32]	1984	Min. gynae.	10	1.25	D > M*	D > M
[69]	1986	Female orthop.	20	1.25	D > M	NR
[89]	1986	Maj. gynae.	10	2.5	D > M	ns
[101]	1989	Min. gynae.	5–10	Various	D > M	ns

TABLE X. *Approximate pharmacokinetic values for drugs used in the prevention and treatment of PONV.* $T_{\frac{1}{2}}$ *= Elimination half-life; Vd = volume of distribution; Clearance (Cl) = total body clearance. *Variable first-pass metabolism. NA = Not available*

Drug	$T_{\frac{1}{2}}$ (h)	*Vd* (litre kg^{-1})	*Cl* (ml min^{-1} kg^{-1})	Absorption		Reference
				Oral	I.m.	
Metoclopramide	4	2.2	10	Good*	Good	[8, 28, 62, 112]
Prochlorperazine	7	21	2.7	Poor	NA	[125]
Perphenazine	9	20	1.8	Poor	Good	[60]
Droperidol	2	1.6	10	Good	Good	[35, 52, 80, Janssen Pharmaceuticals]
Hyoscine	2–4	1.2	15	Fair	Good	[98, 105, 107]
Atropine	2–4	1.3	6	Good	Variable	[68]

Metoclopramide and droperidol

It has been suggested previously in this review that metoclopramide has not shown reliable efficacy; comparisons of metoclopramide and droperidol are consistent with this. Several recent well controlled comparative studies are available [32, 69, 73, 89, 101] and are summarized in table IX. The efficacy of droperidol in four of five or these studies was significantly greater than metoclopramide. Cohen, Woods and Wyner [32] failed to demonstrate statistical significance but there was a definite trend (nausea: placebo 60 %; metoclopramide 64 %; droperidol 41 %) and the power of the study was small (30 patients in each group).

However, these data suggest that improved efficacy may be at the expense of prolonged recovery from anaesthesia (table IX). Statistically significant prolongation of recovery was reported in two of the four studies which measured this variable.

Other comparisons

There are only a few studies which have compared other combinations of antiemetics and these are over 20 years old. Metoclopramide and perphenazine were compared by Handley [59], and Lind and Breivik [82]. Metoclopramide 10 mg or perphenazine 5 mg was given i.m. at the end of surgery in patients undergoing minor gynaecological surgery [59]. Both drugs were far superior to placebo but there was no difference between them in efficacy (perphenazine 96 % no PONV; metoclopramide 92 %; placebo 60 %). However, Lind and Breivik [82] found metoclopramide 10 mg more effective than perphenazine 5 mg in patients undergoing gynaecological laparoscopies. Treatment was given at the end of operation and both mean nausea scores (1.7 *vs* 3.4) and incidence of retching and vomiting (12.6 % *vs* 26.9 %) were reduced in the metoclopramide group. However, recovery time was significantly greater in the metoclopramide group (22 min *vs* 16 min). No firm conclusions can be based on these two early studies and more work is needed if the relative efficacy of metoclopramide and perphenazine is to be defined.

One of the first investigations into the efficacy of metoclopramide in PONV compared metoclopramide 20 mg and prochlorperazine 10 mg given i.m. at the end of surgery [128]. Both treatments were superior to placebo and metoclopramide was significantly better than prochlorperazine (PONV: placebo 38 %; prochlorperazine 19 %; metoclopramide 7 %). Recovery times were not affected and there was no difference in the incidence of side effects.

The efficacy of prochlorperazine 12.5 mg, cyclizine 50 mg and perphenazine 5 mg were compared by Robbie in 1959 [111]. This study was not well controlled but involved over 500 patients. The incidence of PONV in the "control" group was 19 %, and after perphenazine 7 %, prochlorperazine 11 % and cyclizine 13 %. Mean recovery times were increased in the perphenazine and cyclizine groups (22.3 min and 24.5 min, respectively compared with control (18.5 min)). The statistical significance of these data is difficult to assess.

The relative efficacies of droperidol 5 mg and prochlorperazine 10 mg in the treatment of established PONV was assessed by Loeser and colleagues in 1979 [83]. Both were more effective than placebo. However, onset of action of droperidol tended to be later than prochlorperazine but duration of action was longer.

CONCLUSION

The literature enables some conclusions to be made regarding current treatment of PONV. Metoclopramide is a popular antiemetic but its performance in well controlled clinical trials is disappointing. There seems to be no indication for i.v. administration of metoclopramide at induction of anaesthesia for the prevention of PONV. The literature indicates that droperidol is more effective than metoclopramide. Chlorpromazine and perphenazine are effective also, but modern well designed studies confirming this would be welcome. The limited data available on cyclizine indicate efficacy and it would be worthwhile investigating this drug further. Transdermal hyoscine has been proven to be of benefit in several studies and perhaps its more widespread use should be encouraged in order to ascertain its true role in the prevention of PONV.

Extrapyramidal reactions are uncommon but extremely unpleasant. However, the less spectacular problem of agitation and apprehension noted in some studies is likely to be more frequent and this should be investigated further. Sedation is a frequent finding, but apart from day-case surgery, this is not likely to be a significant problem in most patients. Despite these and other side effects, it should be remembered that many millions of patients have been treated safely with these drugs.

However, it is clear that, despite being better than placebo, the efficacy of currently available antiemetics is often poor. Many patients continue to experience severe PONV. Two important factors contribute to this failure. There are many causes of PONV and antagonizing only dopaminergic or cholinergic receptors is not sufficient in many patients. Further research is needed in this area. The development of 5-HT_3 receptor antagonists is likely to be a considerable advance in the treatment of PONV.

Antiemetics are often not administered effectively. An appreciation of the enormous variability in the pharmacokinetics of opioids has led to the development of drug delivery systems such as variable rate infusions and PCA. In contrast, there has been little interest in the pharmacokinetics of antiemetics and clearly this is an important consideration in many cases of therapeutic failure. Pharmacokinetics of these drugs are summarized in table X. Perhaps greater emphasis should be placed on the pharmacokinetic variability of these drugs in order to optimize delivery of antiemetic therapy in the postoperative period.

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THE ROLE OF 5-HT IN POSTOPERATIVE NAUSEA AND VOMITING

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The discovery of potent, selective, 5-HT_3 receptor antagonists (see [17] for review) and the demonstration of their potent antiemetic activity in experimental animals [23] and man [6], has generated considerable interest in the control of the emetic reflex response. Indeed, selective 5-HT_3 receptor antagonists are now used clinically to control emesis induced by chemotherapy or radiotherapy in cancer patients and in postoperative nausea and vomiting (table I).

Both peripheral and central mechanisms are involved in the control of emesis [1]. Evidence for the involvement of 5-HT and 5-HT_3 receptors in such mechanisms is derived from experiments: in the periphery, from measurement of concentrations of 5-HT and 5-HIAA in the gastrointestinal mucosa or urine [12], and from the effects of 2-methyl-5-HT (5-HT_3 receptor agonist) and ondansetron on afferent vagal discharge in the ferret [1]; and in the CNS, from experiments in which the antiemetic effects of 5-HT_3 receptor antagonists have been established after direct injection into the brain stem [15].

Although 5-HT_3 receptor antagonists are potent inhibitors of emesis induced by cytotoxic drugs and radiation, such compounds also exhibit antiemetic activity against a wide spectrum of emetic challenges, thus implicating 5-HT_3 receptors in the broad control of the emetic reflex (table II).

These general antiemetic properties of the 5-HT_3 receptor antagonists, and of ondansetron in particular, led to the clinical evaluation of ondansetron in postoperative nausea and vomiting (PONV). In contrast to the emetic responses to cytotoxic chemotherapy and radiotherapy, relatively little is known about the mechanisms involved in the control of PONV and discussion of such mechanisms is necessarily speculative. Thus, the present discussion considers the mechanisms elucidated from studies using cytotoxic drugs and radiation, and attempts to draw analogies with possible events associated with anaesthesia and surgery. The control of the vomiting reflex is complex, involving both afferent and efferent pathways in the brain stem and also higher centres and the vestibular apparatus [10]. Our present understanding of the control of emesis is derived principally from studies on the afferent arm, involving both peripheral and central neuronal circuits, and the present discussion concentrates principally on these latter pathways.

5-HT_3 RECEPTORS AND PONV

Peripheral pathways

Emesis induced by cytotoxic drugs and radiation is associated with damage to the gastrointestinal mucosa [5, 27] and the mobilization of 5-HT from mucosal enterochromaffin cells [9, 13]. This 5-HT probably excites 5-HT_3 receptors on mucosal vagal afferents, thereby activating the afferent arm of the vomiting reflex [1]. Indeed, emesis induced by

TABLE I. *Present status of 5-HT_3 receptor antagonists as antiemetics. All compounds are potent, 5-HT_3 receptor antagonists with a selectivity ratio of at least 1000 compared with other receptor types [12]*

Compound	Approval	Formulations available
Ondansetron	Emesis induced, by cytotoxic chemotherapy, radiotherapy and PONV	I.v. and oral
Granisetron	Emesis induced by cytostatic therapy	I.v.
Tropisetron	Emesis induced by cancer chemotherapy	I.v. and oral

TABLE II. *Antiemetic profile of 5-HT_3 receptor antagonists. (* Inhibition of $CuSO_4$-induced emesis by 5-HT_3 antagonists is not a consistent finding (see [8])*

Emetic challenge	Species	5-HT_3 antagonist	Reference
$CuSO_4$	Ferret	Ondansetron	[11]
	Ferret	Granisetron	[1]
Ipechacuanha	Ferret	Tropisetron	[8]
	Man	Ondansetron	[20]
Emetin	Ferret	Renzapride	[1]
Peptide YY	Dog	Zacopride	[24]

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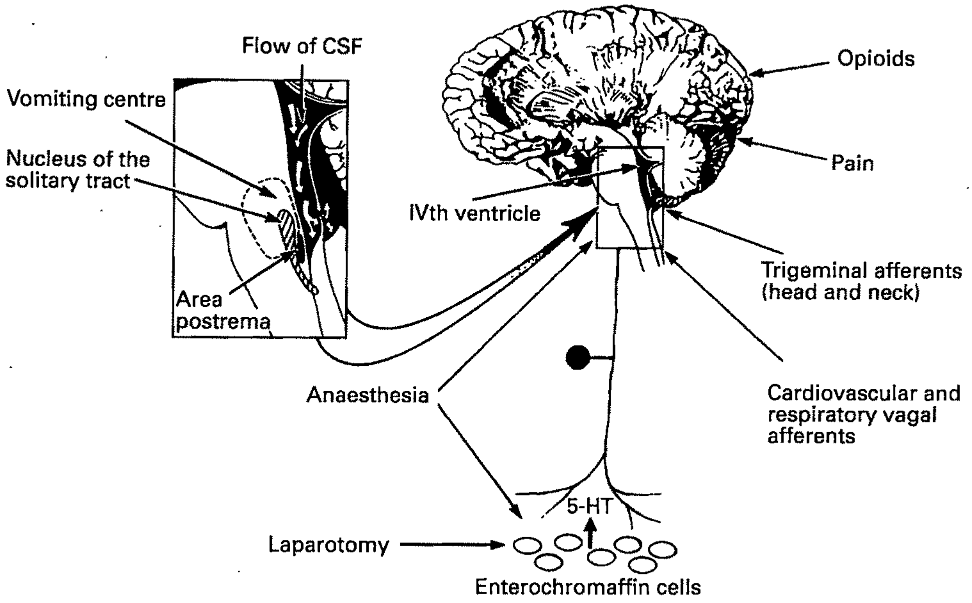
Flow of CSF
Vomiting centre
Nucleus of the solitary tract
Area postrema
IVth ventricle
Opioids
Pain
Trigeminal afferents (head and neck)
Cardiovascular and respiratory vagal afferents
Anaesthesia
5-HT
Laparotomy
Enterochromaffin cells

FIG. 1. Proposed scheme summarizing the peripheral and central mechanisms involved in the control of emesis.

cytotoxic drugs and radiation in the ferret is ameliorated by vagotomy [2, 14].

Several surgical procedures may also affect these peripheral afferent pathways. The anaesthetic itself could disrupt mucosal enterochromaffin cells and induce release of paracrine transmitters, including 5-HT, resulting in afferent vagal firing and initiation of the vomiting reflex. A similar mechanism of cell disruption may be induced also by gastrointestinal distention caused by diffusion of nitrous oxide into the lumen of the gastrointestinal tract [7]. In addition, laparotomy, involving manipulation and irritation of the gastrointestinal tract, could activate vagal afferents via mucosal 5-HT release. Although these peripheral mechanisms are speculative, the involvement of 5-HT from enterochromaffin cells is likely and would provide a rational explanation for the antiemetic effect of ondansetron in PONV.

It is particularly interesting to speculate on how other peripheral systems, outside the gastrointestinal tract, may interact with the emetic pathways to modify the vomiting reflex. Gastric vagal afferents terminate principally in the medial subnucleus of the tractus solitarius [16] and vagal afferents from other abdominal and thoracic systems, namely the heart and respiratory tract, also terminate in distinct, adjacent regions of the nucleus tractus solitarius [16]. Therefore, it is possible that central connections exist between these "nuclei" controlling gastrointestinal, cardiac and respiratory function. Thus cardiovascular or respiratory perturbations, arising principally from hypertension and hypoxia, with or without tracheal irritation associated with surgery and anaesthesia, may sensitize the vomiting system through neuronal pathways involving 5-HT of central origin and 5-HT$_3$ receptors. On this basis, ondansetron would attenuate these responses. However, it must be pointed out that endogenous 5-HT and 5-HT$_3$ receptors do not appear to be involved directly in the control of cardiovascular or respiratory function as ondansetron has no effect on these systems [19, 26].

It has been noted that patients undergoing surgery in the head and neck region are particularly susceptible to PONV [7]. In this context, it is known that sensory afferent fibres of the trigeminal nerve (the largest cranial nerve and predominantly sensory) terminate in the nucleus tractus solitarius [3], and 5-HT$_3$ receptors are present in the spinal trigeminal nerve complex [4]. Thus, we may speculate that surgery in the region of the head and neck sensitizes the nucleus tractus solitarius to induce a vomiting response via stimulation of trigeminal afferents. This sensitization of the nucleus tractus solitarius involves 5-HT pathways and 5-HT$_3$ receptors because ondansetron is effective in controlling this aspect of PONV.

Central pathways

Gastrointestinal vagal afferents terminate in the area postrema and nucleus of the solitary tract and these two medullary structures are known to be important in the control of the vomiting reflex; indeed the area postrema is the locus of the chemoreceptor trigger zone [1]. Furthermore, the area postrema and nucleus tractus solitarius contain a high concentration of 5-HT$_3$ receptors [22] which are located on presynaptic terminals [18, 21]. Block of these central 5-HT$_3$ receptors by the discrete injection of ondansetron into the region of the area postrema and nucleus tractus solitarius inhibits cisplatin-induced emesis in the ferret [15]. It is therefore pertinent to consider the possible role of the area postrema and nucleus tractus solitarius in the control of PONV.

The area postrema is a circumventricular organ located outside the blood–brain barrier, and is therefore uniquely placed to "sample" both blood and CSF. It is possible that an anaesthetic substance in the blood, CSF, or both, could stimulate neurones (or cause disinhibition of a moderating influence) within the area postrema and activate the vomiting reflex via a 5-HT pathway. Similarly, the anaesthetic could affect the vomiting reflex via 5-HT containing neurones, or interneurones, in the nucleus tractus solitarius and other components in the vomiting system, namely the parvicellular reticular formation and visceral and somatic motor nuclei.

Pain in the postoperative period may also predispose patients to PONV. Painful stimuli from the viscera are transmitted to the CNS in the splanchnic nerves. In this context it is interesting to note that sectioning of the splanchnic nerves in the ferret, while having no effect itself on the emetic response to cisplatin, enhanced the antiemetic effect of vagotomy [14]. Thus it is likely that painful stimuli induce discharge of splanchnic afferents which in turn contribute to the initiation of the vomiting reflex. Because ondansetron completely blocks the emetic response to cisplatin in the ferret [25], it is possible that 5-HT$_3$ receptors are involved in the splanchnic component of the vomiting reflex.

SUMMARY

In this review it has been speculated that PONV is induced by the anaesthetic and by the trauma and perturbations associated with surgery. Indeed, it is unlikely that PONV is caused by any one pathophysiological input, but is multifactorial in origin. These perturbations may be peripheral, central, or both, and involve direct effects on the vomiting system together with afferent inputs in the vagal, splanchnic and trigeminal nerves. A proposed scheme summarizing these inputs is given in figure 1. The precise mechanisms through which 5-HT and 5-HT$_3$ receptors contribute to the control of PONV is unknown, but their involvement is demonstrated by the antiemetic effect of ondansetron.

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5-HT$_3$ ANTAGONISTS IN POSTOPERATIVE NAUSEA AND VOMITING

D. RUSSELL AND G. N. C. KENNY

Postoperative nausea and vomiting (PONV) are distressing side effects of anaesthesia and surgery, with a high incidence after gynaecological surgery [19, 35] and after strabismus surgery in children [21, 26]. An incidence as great as 83% has been reported in female patients after major orthopaedic surgery [22]. Of the antiemetic agents currently available to treat PONV, droperidol would appear to be the most efficacious [22, 35], but despite prophylactic droperidol 2.5 mg 10 min before the end of general anaesthesia for major gynaecological surgery, more than 30% of patients still complained of postoperative emesis [35]. The quest for more effective antiemetic drugs, without the potential for sedative or extrapyramidal side effects has led to the recent development of a relatively new class of drugs, of which ondansetron, granisetron, tropisetron and dolasetron are examples.

PHARMACOLOGY

These drugs are thought to act by highly selective and potent antagonism of 5-hydroxytryptamine$_3$ (5-HT$_3$) receptors in the brain, with a high density of 5-HT$_3$ receptors occurring in the area postrema and the nucleus tractus solitarius, equating with the chemoreceptive trigger zone. In experimental animals given cisplatin, 5-HT$_3$ antagonists administered selectively into the area postrema, produced a significant antiemetic effect compared with controls [18]. Additionally, an increased turnover and release of 5-HT from enterochromaffin cells in the small bowel of the ferret when treated with cisplatin [15] suggests that this might contribute to the emetic effect, possibly by stimulating vagal afferent fibres which in turn cause 5-HT release in the area postrema. It has been postulated, therefore, that the 5-HT$_3$ antagonists may act peripherally in the gastrointestinal tract in addition to having a central site of action within the brain [53].

Known side effects of 5-HT$_3$ antagonists include headache, light headedness, a warm sensation in the epigastrium, flushing and constipation. Indeed, in a study of 10 healthy male volunteers who received ondansetron in relatively high doses [11], Gore and colleagues concluded that the drug slowed colonic transit, as gastric emptying and small bowel transit time were unaffected while whole gut transit time was significantly prolonged; they suggested that ondansetron might even be a useful antidiarrhoeal agent.

PHARMACOKINETICS

Ondansetron may be administered either orally or i.v. The tablets contain 4 mg or 8 mg of ondansetron base as the hydrochloride dihydrate [29]. Studies involving healthy, young, male volunteers have shown that oral bioavailability in man is approximately 60% (single oral or i.v. 8 mg doses produce peak plasma concentrations of 30 ng ml^{-1} and 80 ng ml^{-1}, respectively), with the peak plasma concentration occurring at about 1.5 h after oral administration [4]. Ondansetron is bound to plasma proteins to a moderate extent (70–76%), with a relatively large volume of distribution of approximately 160 litres. Its terminal plasma half-life is approximately 3 h, with only 5% being excreted unchanged by the kidneys. The major route of excretion is by hydroxylation followed by glucuronide or sulphate conjugation in the liver; most of these inactive metabolites appear in the urine [47]. Clearance is 541 ml min^{-1} and is reduced with increasing age, resulting in increased oral bioavailability because of reduced first pass hepatic metabolism, and a prolonged half-life of 5.4 h in those more than 75 yr of age. There is also a significant difference between the sexes, with clearance of the drug occurring more slowly in women than in men [45]. The United Kingdom data sheet for ondansetron states that the dose should be limited to 8 mg in 24 h in those with moderate or severe hepatic impairment, but it is considered unnecessary to vary dosage regimens according to age or sex.

The i.v. preparation [30] is an isotonic aqueous solution containing ondansetron hydrochloride dihydrate 2 mg ml^{-1} buffered to pH 3.5 with sodium citrate and citric acid monohydrate, with a shelf life of 3 yr. It is compatible with 0.9% sodium chloride, 5% glucose and Ringer's lactate solution, and can be administered either by slow i.v. injection or by infusion.

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KEY WORDS
Antagonists, miscellaneous: 5-HT$_3$. Vomiting: nausea.

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constriction in some vascular beds and 5-HT_3 mediated vasodilatation elsewhere. The administration of a 5-HT_3 antagonist might therefore be expected to produce an increase in arterial pressure and a reflex decrease in heart rate. However, when they studied 71 awake female patients allocated randomly to receive ondansetron 0, 1, 4 or 8 mg i.v. over 2 min, heart rate, arterial pressure (systolic or diastolic), ventilatory frequency and oxygen saturation did not change significantly in any group.

Dershwitz and colleagues investigated if ondansetron had any effect on opioid-induced respiratory depression [8]. Alfentanil 5 $\mu g\ kg^{-1}$ was administered to 29 healthy male volunteers, followed by an infusion of 0.25–0.75 $\mu g\ kg^{-1}\ min^{-1}$. Subjects rebreathed from a 13-litre reservoir bag and ventilatory drive was assessed by measurement of end-tidal carbon dioxide at the point where minute volume reached 15 litre min^{-1}. The respiratory depression produced by alfentanil was unaffected by the administration of placebo or ondansetron 8 mg or 16 mg i.v., in a random, double-blind study. Hall and Ceuppens [17] evaluated the effect of repeated oral doses of ondansetron on psychomotor performance in a randomized, double-blind, four-way, crossover study of 12 healthy, male non-smokers each given five doses of oral ondansetron 1 mg, 8 mg or placebo twice daily for 2.5 days. Lorazepam 2 mg, considered to have antiemetic properties and used in some centres as an adjunct antiemetic in chemotherapy patients [12], given as a single oral dose as the fifth dose after four doses of placebo was also assessed. A 12-day drug washout period was used between different regimens. Four tests of psychomotor function (choice reaction time, critical flicker fusion test, simulated car tracking test and Sternberg memory scanning task) were carried out before the first dose and again 3 h after the fifth dose. Both doses of ondansetron did not produce impairment of psychomotor function compared with placebo. In contrast, lorazepam resulted in significant impairment in all the tests except the critical flicker fusion test, where its effect just failed to reached statistical significance.

Leigh, Link and Fell [32] carried out a similar crossover study of the effects of granisetron and lorazepam, alone and in combination, on psychometric performance. Twelve healthy male subjects received an oral dose of either placebo or lorazepam 2.5 mg followed 30 min later by an i.v. infusion of placebo or a relatively large dose of granisetron (160 $\mu g\ kg^{-1}$) over 3 min. Four distinct groups were formed: group 1 received oral and i.v. placebo; group 2 received oral placebo and i.v. granisetron; group 3 received oral lorazepam and i.v. placebo; and group 4 received oral lorazepam and i.v. granisetron. A battery of psychometric tests was carried out 1 h before, and 1.5, 3, 6 and 24 h after the start of the infusion. Granisetron alone did not impair psychometric function, while lorazepam alone produced significant impairment in most of the tests used. There was little evidence of any synergy between the two drugs.

Perhaps more significantly, Lessin and co-workers [33] assessed recovery time in 50 patients allocated randomly to receive either ondansetron 8 mg i.v. or placebo during gynaecological surgery and failed to demonstrate any difference in either time to awakening or cognitive function between the two groups. Kovac and colleagues [25] investigated the effect of placebo or ondansetron 1, 4 or 8 mg administered i.v. before a standardized general anaesthetic for day-case laparoscopy. There was no difference in awakening time, time spent in recovery or hospital discharge time between groups and all patients appeared equally responsive and awake after operation. Pearson and colleagues [40], in a similar study, demonstrated that psychomotor performance was still impaired 2 h after ambulatory surgery, but that the administration of ondansetron 1, 4 or 8 mg i.v. before induction of general anaesthesia did not affect psychomotor performance compared with placebo; and there was no subjective variation in mood.

The 5-HT_3 antagonists are unique among antiemetics in that they have no effect at histaminergic, dopaminergic or cholinergic receptors [53], and can therefore be expected to be devoid of troublesome side effects such as drowsiness, dry mouth, blurring of vision, urinary retention, hyperprolactinaemia, tardive dyskinesia and extrapyramidal effects. The antiemetic effect of metoclopramide is now suspected to be caused partially by antagonism at 5-HT_3 receptors, but its lack of selectivity resulted in its propensity to cause side effects, particularly in high doses in young patients [54]. The 5-HT_3 antagonists, because of their selectivity, however, have no effect on emesis induced by dopamine receptor agonists, or on motion sickness [39].

The side effect and safety profile of ondansetron was reviewed by Smith [49]. The extrapyramidal effects occasionally seen with metoclopramide have not occurred with ondansetron. Significant drug-related side effects attributed to ondansetron include constipation, headache and a warm sensation or flushing on i.v. administration. These occur in only a small proportion of patients and it is clear that ondansetron has a wide therapeutic index in chemotherapy patients.

USE IN ANAESTHESIA

There are several studies comparing ondansetron with placebo in patients undergoing anaesthesia and surgery. Leeser and Lip [31] administered ondansetron 16 mg or placebo orally in a double-blind study approximately 1 h before operation and 8 h later in 84 ASA I-III patients undergoing major intra-abdominal gynaecological surgery under general anaesthesia. The study drug was given with oral diazepam premedication, and anaesthesia was induced with thiopentone and maintained with 67% nitrous oxide and isoflurane in oxygen. Muscular relaxation was provided by vecuronium and analgesia with alfentanil, up to 7.5 mg. At the end of the procedure, neuromuscular block was antagonized with neostigmine and atropine, as necessary. Thereafter, analgesia was provided with morphine, with similar total amounts being administered to both groups. All patients were given prochlorperazine

TABLE II. *Efficacy of oral ondansetron 1, 8 or 16 mg vs placebo, given 1 h before induction of general anaesthesia for major gynaecological surgery, and 8 and 16 h thereafter.* ***$P < 0.001$ *compared with ondansetron 1 mg or placebo* [23]

	Placebo ($n = 247$)	Ondansetron dose (mg)		
		1 ($n = 238$)	8 ($n = 243$)	16 ($n = 245$)
Patients experiencing nausea during first 24 h (%)	75	70	56***	55***
Patients experiencing vomiting during first 24 h (%)	60	55	37***	37***

25 mg per rectum if required and assessments of nausea and vomiting were made at 1 and 24 h after operation. One hour after recovery, 52 % of the placebo group complained of nausea and 40 % had vomited, compared with 17 % and 12 %, respectively, in the ondansetron group. Over the first 24 h after operation, 67 % of the placebo group complained of nausea with 60 % vomiting, compared with 29 % and 26 %, respectively, in the ondansetron group. All these differences were statistically significant. Thirty-three doses of prochlorperazine were administered to 22 placebo patients, compared with 12 doses given to eight of those who had received ondansetron. There were no significant cardiorespiratory effects during the study and there was no significant difference in the recovery time after anaesthesia. Three patients in the ondansetron group and one patient in the placebo group developed minor increases in liver function tests. They concluded that ondansetron was a promising agent for the prevention of PONV and that further studies would be required to establish its optimal dose.

In a major multicentre study involving 995 ASA I–III patients undergoing major gynaecological surgery, Kenny and co-workers [23] compared the efficacy of ondansetron 1, 8 or 16 mg orally, or placebo, given 1 h before operation with benzodiazepine premedication, with further doses administered at 8 and 16 h. The general anaesthetic technique was largely standardized and after operation, morphine with or without prochlorperazine or metoclopramide was administered as required. There were significant differences in the incidence and degree of nausea, and the incidence and median time to first episode of vomiting during the first 24 h after operation between those who had received ondansetron 8 and 16 mg and those who had received either ondansetron 1 mg or placebo (table II), with the higher doses producing more favourable results. However, there were no statistically significant differences for any of the variables between those receiving ondansetron 1 mg or placebo, or between those receiving ondansetron 8 or 16 mg. There were no clinically significant cardiorespiratory effects, or any differences in the recovery time after anaesthesia. Increases in aminotransferase concentrations occurred in up to 20 % of patients, with the incidence only slightly higher in the ondansetron treated patients compared with the placebo group. From the results of this study, one can conclude that ondansetron 8 mg given 1 h before operation and 8 and 16 h thereafter, produced a significantly greater antiemetic effect than ondansetron 1 mg or placebo, but that increasing the dose to 16 mg 8-hourly conferred no additional benefit.

Several studies have confirmed the efficacy of i.v. ondansetron in the treatment and prophylaxis of postoperative nausea and vomiting. Larijani and colleagues [28] studied 36 patients, mainly female, suffering from nausea and vomiting after orthopaedic and gynaecological surgery, allocated randomly to receive either ondansetron 8 mg i.v. or placebo, in a double-blind study over 2–5 min. Ondansetron was significantly more effective than placebo and control of nausea was achieved in 78 % of the ondansetron patients compared with 28 % of controls. There were no significant adverse effects. Bodner and White [1] studied 71 healthy females who had developed nausea and vomiting after laparoscopy, and allocated them randomly in a double-blind study to receive either ondansetron 8 mg i.v. or placebo. Forty-nine percent of the ondansetron patients, compared with 8 % of the placebo group, had no further emetic episodes, while 43 % and 86 %, respectively, required rescue antiemetics. Cardiorespiratory variables and sedation scores were not significantly different between the two groups.

Several small studies [9, 34, 46] have demonstrated that the administration of ondansetron 8 mg i.v.before induction of anaesthesia and again 8 h later, is more effective than placebo in preventing nausea and vomiting in surgical patients, without significant side effects. In a double-blind, placebo-controlled study involving 179 female patients undergoing day-case laparoscopy, Wetchler and colleagues [55] demonstrated that a single dose of ondansetron 8 mg given i.v. before induction of anaesthesia was associated with a significantly smaller number of postoperative emetic symptoms compared with a control group. Seventy-six percent of the ondansetron group experienced no emetic symptoms during the first 2 h after surgery, compared with 58 % of the placebo group. In the next 22-h period, 69 % of the treatment group were devoid of emetic symptoms, compared with 49 % of controls. Kovac and colleagues [24] described a large, multicentre study designed to assess the optimal dose of i.v. ondansetron for surgical patients. Five hundred and eighty ASA I-II females undergoing laparoscopy under general anaesthesia were enrolled in the study. The patients were stratified into two groups, those with a positive or negative history of nausea and vomiting after general anaesthesia, and allocated randomly to receive ondansetron 1, 4 or 8 mg, or placebo by i.v. infusion over 2–5 min before induction of anaesthesia with thiopentone, methohexitone or thiamylal. Intraoperative analgesia was provided with fentanyl or alfentanil, neuromuscular block with suxamethonium, vecuronium or atracurium, and after tracheal intubation, anaesthesia was maintained with isoflurane and nitrous oxide in oxygen. At the end of operation, neuromuscular

TABLE III. *Efficacy of a single i.v. dose of ondansetron 1, 4 or 8 mg, or placebo given before induction of general anaesthesia for laparoscopy for the group as a whole and also when subdivided into those with a positive (+ve) and negative (−ve) history of nausea and vomiting after general anaesthesia *P < 0.05; **P < 0.01 compared with placebo [24].*

	Placebo	Ondansetron dose (mg) 1	4	8
Patients experiencing nausea during first 24 h (%)				
All patients	71	69	58*	44*
+ve history	95	86	70*	54*
−ve history	60	62	52	39**
Patients experiencing vomiting during first 24 h (%)				
All patients	54	38*	24**	23**
+ve history	75	57	45*	28**
−ve history	44	30*	14**	20**

block was antagonized with neostigmine or edrophonium, and atropine or glycopyrronium. All ondansetron doses, especially 4 mg and 8 mg, were significantly more effective than placebo in preventing emesis over the whole 24-h recovery period (table III), with a similar incidence of side effects, such as headache and dizziness, in the ondansetron groups compared with the placebo group; ondansetron did not appear to have any significant effect on vital signs or laboratory values. The optimal dose was considered to be 4 mg, with 8 mg perhaps offering added benefit for those with a past history of nausea and vomiting after general anaesthesia.

The results of comparative studies with other antiemetics are awaited, but ondansetron has clearly been shown to be effective and safe in the prophylaxis and treatment of postoperative nausea and vomiting compared with placebo treatment and a product licence has been issued recently in the United Kingdom for ondansetron to be used for this indication. The data sheet recommends that ondansetron 8 mg should be administered orally 1 h before surgery, followed by two further doses of 8 mg at 8-hourly intervals. Alternatively, a single dose of 4 mg may be given by slow i.v. injection at induction of anaesthesia. For the treatment of established postoperative nausea and vomiting, a single dose of 4 mg given by slow i.v. injection is recommended. These dosage regimens are appropriate when one considers the results of the research reviewed in this paper [23, 24].

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